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MAGNETIC RESONANCE IMAGING FOR THE ANALYSIS OF  
HUMAN GASTRIC MOTOR ACTIVITY,  
INTRAGASTRIC DISTRIBUTION AND RELATED EMPTYING

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# Summary

The mechanical function of the stomach plays a central role in nutrition and delivery of orally administered drugs. Control of nutrient delivery into the small intestines is achieved over wide ranges of gastric volumes and nutrient compositions by the coordinated stimulation or inhibition of active pumping and flow resisting motor mechanisms.<sup>1</sup> Hormonal or autonomic feedback signals from the small intestine (chemo- and mechanoreceptors) are the dominant control mechanisms of mechanical activity of the stomach.<sup>2,3</sup> The relative contribution of the three potential motor mechanisms determining the rate of gastric emptying, i.e. pressure pump,<sup>4,5</sup> peristaltic pump<sup>4</sup> and pyloric resistance,<sup>6</sup> to gastric emptying is still controversial. So far, these driving forces have been insufficiently delineated in humans and solely investigated with invasive methods such as intraluminal manometry and gastric barostat. These techniques however, do not provide data on emptying rates, stomach and gastric air volumes and intragastric meal distribution and therefore need to be combined with imaging techniques.<sup>4,7</sup>

Magnetic resonance imaging (MRI) has evolved as the imaging modality of choice for the detection of soft tissue tumours<sup>8-11</sup> and the diagnosis of brain function<sup>12</sup> and diseases.<sup>13</sup> Because of the fast and continuous improvements in MRI gradient technology over last years, the innovative sequencing and the advent of parallel imaging (a recently introduced rapid imaging method), MRI has recently been recognised as powerful and inevitable method for high quality imaging of human organ function. Therefore, MRI was also introduced and evaluated for the use in gastrointestinal (GI) research, i.e. the measurement of gastric emptying, secretion and motility and the intragastric distribution of macronutrient and specific MRI marker.<sup>14-19</sup> The non-invasive character, the flexible and excellent soft tissue contrast and the real-time capabilities of this technique make MRI an almost 'ideal' method for the investigation of human GI function.<sup>20</sup>

The first studies, described in chapter 2, aimed on introducing MRI as a valid and non-invasive tool for pharmaceutical research in humans, i.e. to develop and evaluate MRI based methods for the monitoring and assessment of the *in vivo* performance of oral drug delivery systems. These projects studied the feasibility of two different MRI markers for tablet labelling and analysed the intragastric position, residence time and movement of different orally administered tablets as well as the meal dependency of intragastric tablet performance. Also, the dependency of the tablet *in vivo* performance on meal composition and the time point of administration was successfully determined. Data showed that the labelling of tablets with  $Fe_3O_4$  and  $Gd$ -DOTA is feasible and that visualisation and quantification of tablet residence time, floating/sinking performance and the intragastric release and distribution of the drug model  $Gd$ -DOTA within the human stomach can be

reliably performed using MRI. Results supported previous findings that gastro-retention of tablets is closely related to their overall size, but also showed that even size is no safe parameter for controlled retention, since exceptions exist due to anatomical and physiological variations.

This was the first investigation demonstrating the feasibility of MRI to study the impact of formulation density and size and meal emptying on the dynamics and behaviour of ingested gastric-retentive tablets in the human stomach. This knowledge is of paramount importance for controlling and improving the effectiveness and bioavailability of orally administered drugs and studying the gastrointestinal pharmacodynamics and kinetics. Studies demonstrated that MRI has the potential to replace  $\gamma$ -scintigraphy (the current gold standard) in this research field and highlighted that commonly performed *in vitro* or animal studies alone will not be sufficient to reliably predict these parameters in the human body.

The second set of studies, described in chapter 3, comprised the development of MRI techniques, applicable to MRI systems of different architecture and field strength, allowing simultaneous assessment of important mechanical parameters of human gastric function in various body positions. The physiological aim was to extend and improve the understanding of the (above mentioned) potential driving forces and regulatory mechanisms (pressure pump, peristaltic pump and pyloric resistance) of human gastric emptying. Imaging protocols were developed for a 0.5 Tesla open-configuration and/or a 1.5 Tesla whole-body MRI system and gastric motor function and emptying was investigated and compared in the upside down (UDP), the right decubitus lying (RP) body position and normal post-prandial, i.e. seated position (SP). In addition, gastric volume response and sensory response of the gastric system (in SP and RP) after ingestion of different macronutrient (fat, glucose, protein) was analysed. Data provided further support to the hypothesis that the stomach rather resembles a ‘pressure pump’ (low-pressure tonic contractions of the stomach with the formation of a gastro-duodenal pressure gradient) than a ‘peristaltic pump’ (propagating high-pressure waves). Small changes were observed in the volume responses and emptying patterns for the different positions. These alterations in gastric physiology may not be considered of clinical relevance, since the changes usually observed for meal emptying in patients diagnosed with gastroparesis are of much larger extend. However, the capability to detect such subtle differences, in a physiological process of large inter-individual variation, highlights the excellent sensitivity of MRI for the diagnostic imaging of gastric (patho-)physiology.

For the first time, the most important mechanical parameters of human gastric motor function were measured and analysed simultaneously and their dependency on body position were investigated. Also for the first time, the relationship and the posture dependency of the human gastric volume and sensory response to the three different macronutrient, administered as isocaloric meals, was analysed. Data demonstrated that gastric MRI performed in the right decubitus lying body position is feasible for GI clinical research on gastric motor function and diagnosis of gastroparesis and gastric motility disorders.

This thesis report reinforces the large potential of MRI for the non-invasive measurement and evaluation of gastric physiology and a variety of pathophysiologicals and anticipates this powerful and flexible imaging technique as the future “method of choice” for the assessment of GI function in humans.



# Zusammenfassung

Die Mechanik des Magens spielt eine zentrale Rolle in der Ernährung wie auch der oralen Einnahme von Medikamenten. Eine koordinierte Stimulation oder Hemmung aktiver Pumpfunktionen und Ausflusswiderstände des Magens ermöglicht eine kontrollierte Abgabe des verarbeiteten Nahrungsbreis in den Dünndarm.<sup>1</sup> Rückwirkend hormonelle oder autonome Signale des Duodenums bzw. Dünndarms (mittels Chemo- und Mechanorezeptoren) sind hierbei die wohl bedeutendsten Kontrollmechanismen der Magenaktivität.<sup>2,3</sup> Die Bedeutung und das Mitwirken der drei prinzipiellen Mechanismen zum Antrieb und zur Regelung der Magenentleerung, nämlich das Prinzip der Druckpumpe,<sup>4,5</sup> das Prinzip der Peristaltikpumpe<sup>4</sup> und das Prinzip des Pyloruswiderstands,<sup>6</sup> sind immer noch umstritten. Bis jetzt wurden diese Mechanismen, welche die treibenden Kräfte der Magenentleerung darstellen, nur ungenügend im Menschen untersucht und beschrieben und fast ausschliesslich mittels invasiver Methoden wie intraluminaler Manometrie und Magenbarostat untersucht. Diese Technologien liefern jedoch keinerlei Informationen über Magenentleerung, Magen- und Mahlzeitvolumen und Mahlzeitverteilung im Magen und müssen daher mit bildgebenden Verfahren kombiniert werden.<sup>4,7</sup>

Die Magnetresonanzbildgebung hat sich zum bildgebenden Verfahren der Wahl bei der Detektion von Tumoren des Weichteilgewebes<sup>8-11</sup> und der Diagnose von Hirnfunktionen<sup>12</sup> und Gehirnkrankheiten<sup>13</sup> entwickelt. Wegen der schnellen und kontinuierlichen Verbesserung der MRI Gradiententechnologie, der innovativen Sequenzentwicklung und der Einführung der parallelen Bildgebung wurde MRI nun als leistungsstarke und unumgängliche Methode zur hochauflösenden Visualisierung menschlicher Organfunktion anerkannt. MRI wurde deshalb bereits in die gastrointestinale (GI) Forschung eingeführt und für die Messung der Magenentleerung, -sekretion und -motilität und der intragastralen Verteilung von Nährstoffen und spezifischen MRI-Markern evaluiert.<sup>14-19</sup> Die Nichtinvasivität, der flexible und exzellente Kontrast für Weichteilgewebe und die Möglichkeit der Echtzeit-Bildgebung dieser Technik machen MRI zu einer fast idealen Methode zur Untersuchung von menschlicher GI Funktion.<sup>20</sup>

Die ersten in Kapitel 2 beschriebenen Studien zielten darauf ab, MRI als wertvolles und nicht invasives Verfahren in die pharmakologische Forschung einzuführen, indem eine MRI basierte Methode zur Verfolgung und Beurteilung des *in vivo* Verhaltens oraler Transportsysteme für Medikamente entwickelt und evaluiert wurde. Diese Studien untersuchten die Anwendbarkeit zweier verschiedener MRI Kontrastmittel für die Tablettenmarkierung und analysierten die intragastrale Position, Verweildauer und Bewegung oral verabreichter unterschiedlicher Tablettenformen sowie deren mahlzeitabhängiges Verhalten. Ausserdem wurde auch die Abhängigkeit des *in vivo* Verhaltens der Tablette von der

Mahlzeitzusammensetzung und des Zeitpunktes der Tabletteneinnahme erfolgreich bestimmt. Die Daten verdeutlichen die Anwendung von  $Fe_3O_4$  und  $Gd$ -DOTA als neutrale MRI-Markierung gastro-retentiver Tabletten, welche die zuverlässige Visualisierung und Quantifizierung der Verweildauer, des Schwimm- und Sinkverhaltens der Tabletten sowie die Abgabe und Verteilung eines Medikamentenmodells ( $Gd$ -DOTA) im menschlichen Magen erlauben. Die Resultate bestärken frühere Ergebnisse, welche zeigten, dass die Gastoretention von Tabletten in enger Beziehung zu deren Grösse steht. Sie zeigen jedoch auch, dass die Tablettengrösse kein sicherer Parameter für eine kontrollierte Magenverweilzeit darstellt, da Ausnahmen aufgrund anatomischer und physiologischer Variabilität existieren.

Dies war die erste Studie, welche die Anwendung von MRI zur Studie der Auswirkungen von Tablettengrösse und -dichte sowie von Mahlzeitentleerung auf die Dynamik und das Verhalten verabreichter gastro-retentiver Tabletten im menschlichen Magen demonstrierte. Solches Wissen ist von enormer Bedeutung, um die Effektivität und biologische Verfügbarkeit oral verabreichter Medikamente zu kontrollieren bzw. zu verbessern und die GI Pharmadynamik und/oder -kinetik zu studieren. Im weiteren verdeutlichen die Ergebnisse dieser Studien auch, dass *in vitro*- oder Tierversuche, wie sie üblicherweise zur Beurteilung von Tablettensystemen durchgeführt werden, nur ungenügende Erkenntnisse über das tatsächliche Verhalten dieser Systeme im Menschen liefern können.

Das zweite in dieser Arbeit vorgestellte Studienprojekt zielte darauf ab, die wichtigsten mechanischen Parameter der menschlichen Magenfunktion in verschiedenen Körperhaltungen gleichzeitig zu analysieren und somit das Verständnis über die oben genannten treibenden Kräfte der menschlichen Magenentleerung (Druckpumpe, Peristaltikpumpe und Pyloruswiderstand) und deren Kontrollmechanismen zu erweitern und zu verbessern. Zu diesem Zweck wurden zunächst vergleichbare MRI-Messprotokolle für zwei verschiedene MRI-Scanner entwickelt, nämlich für ein 0.5 Tesla offenes MRI-System und ein 1.5 Tesla Ganzkörper-MRI-System. An beiden Systemen wurde dann die menschliche Magenmotorfunktion und -entleerung in *Kopf über* Position (UDP - upside down position) und in rechter Seitenlage (RP - right decubitus position) gemessen und mit der normalen Essposition, also der aufrecht sitzenden Position (SP - seated position) verglichen. Zudem wurde in diesem Projekt die Volumenantwort des Magens und die sensorische Antwort des gastrischen Systems (in SP und RP) nach Einnahme verschiedener Grundnährstoffe (Fett, Glukose, Protein) untersucht.

Die Daten dieser Studien unterstützen die Hypothese, dass der Magen eher nach dem Prinzip der Druckpumpe (schwache tonische Magenkontraktionen mit dem Effekt eines sich aufbauenden gastro-duodenalen Druckgradienten) als dem der Peristaltikpumpe (distal bewegende, stark einschnürende Kontraktionen, welche kurzfristig hohe Druckwellen erzeugen) funktioniert. Dies wurde grösstenteils durch die Beobachtung bestätigt, dass die peristaltische Magenaktivität keinen Einfluss auf die Entleerungsgeschwindigkeit zu haben scheint. Es wurden unterschiedliche Entleerungsmuster für UDP im Vergleich zu SP beobachtet. Dies deutet auf Änderungen in den treibenden Kräften der Magenentleerung in dieser Position hin. Diese Veränderungen sind wahrscheinlich auf die sich radikal geänderte Mahlzeitverteilung im Magen und den somit stark unterschiedlichen hydrostatischen Druck im Magen zurückzuführen. Eine Änderung der Mahlzeitverteilung im Magen wurde auch für RP festgestellt, was wiederum leichte Unterschiede in der Dynamik der Entleerung und auch der Volumina verursachte. Diese Unterschiede waren jedoch

klein und wurden als klinisch nicht relevant angesehen, da die üblicherweise beobachteten Veränderungen dieser Parameter in Patienten mit Gastroparese wesentlich grösser sind. Die Erfassung solcher feinen Unterschiede, in einem physiologischen Prozess von grosser inter-individueller Variation, zeigt die exzellente Sensitivität von MRI für die diagnostische Bildgebung gastrischer (Patho-)Physiologie. Für die Grundnährstoff-Studie wurde eine optimierte Analyse-methode zur Bestimmung der Charakteristik der Magenentleerung von Nährstofflösungen angewendet, um die Entleerungskurven von Magen und Mahlzeit zu modellieren und mögliche Unterschiede in der Dynamik von Magenakkommodation und Entleerung zu detektieren. Die Volumenantwort des Magens und die sensorische Antwort des gastrischen Systems auf die Fett-, Glukose- und Protein-Mahlzeiten sowie entsprechende Magenentleerungen waren unabhängig von der Körperposition (SP versus RP). Es wurden auch keine Unterschiede in der sensorischen Antwort für Völlegefühl, Sättigkeit und Blähungen zwischen den Grundnährstoffen gefunden. Unterschiede zwischen den Nährstoffen wurden jedoch detektiert für Magenakkommodation, Magen- und Mahlzeit-dynamik und Entleerungsgeschwindigkeit. Obwohl die (nicht invasiv) gemessenen MRI Daten nicht uneingeschränkt mit denen aus üblich verwendeten invasiven Methoden verglichen werden können, zeigen diese Ergebnisse dennoch erneut die überlegene Sensitivität von MRI zur vollständigen Erfassung der Magenmotorfunktion, welche unter Einbeziehung optimierter Analysemethoden weiter verbessert werden kann.

In diesem zweiten Forschungsprojekt wurden zum ersten Mal die wichtigsten mechanischen Parameter der menschlichen Magenfunktion gleichzeitig erfasst und analysiert und deren Abhängigkeit von der Körperhaltung untersucht. Ausserdem wurde die Beziehung und auch die Positionsabhängigkeit der Volumenantwort und der sensorischen Antwort des Magens zu den in isokalorischen Mahlzeiten verabreichten Grundnährstoffen studiert. Die gewonnenen Daten zeigen, dass auch in rechter Seitenlage durchgeführtes Magen-MRI uneingeschränkt für die klinische Forschung der menschlichen Magenmotorfunktion und auch für die Diagnose von Gastroparese und Magenmotilitätsstörungen angewendet werden kann.

Diese Dissertationsarbeit bekräftigt das grosse Potential von MRI zur nicht invasiven Messung und Evaluierung von normaler und abnormaler Magenphysiologie und antizipiert diese leistungsfähige und flexible Bildgebungstechnik als die zukünftige Methode der Wahl zur Beurteilung menschlicher gastrointestinaler Funktion.

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# Introduction

The mechanical function of the stomach plays a central role in nutrition and delivery of orally administered drugs. Control of nutrient delivery into the small intestines is achieved over wide ranges of gastric volumes and nutrient compositions by the coordinated stimulation or inhibition of active pumping and flow resisting motor mechanisms.<sup>1</sup> Hormonal or autonomic feedback signals from the small intestine (chemo- and mechanoreceptors) are the dominant control mechanisms of mechanical activity of the stomach.<sup>2,3</sup> Many patients suffer nutritional problems with corresponding (significant) symptoms due to the derangement of the close working relationship between the stomach and the small intestine. The most frequent abnormality is slow delivery of nutrient to the small intestine, i.e. gastroparesis or dyspepsia.<sup>7</sup>

Disordered gastric motility, particularly gastroparesis, is a substantial and underrecognised problem in clinical practice. The slow nutrient delivery often results in severe, chronic nausea and vomiting, bloating, fullness, early satiety or abdominal pain<sup>21</sup> that available drugs may not adequately control. In patients diagnosed with diabetes, gastroparesis has an adverse impact on nutrition and the control of blood glucose concentration.<sup>22</sup> Statistics show that 30% to 50% of patients with diabetes eventually develop gastroparesis (6.3% of the United States population have diabetes). Furthermore, not only is gastroparesis an important entity on its own, it also contributes to symptoms in patients with gastroesophageal reflux (GERD), a nonulcer dyspepsia, and intestinal pseudo-obstruction. Statistics from the U.S. Department of Health and Human Services indicate that about 7 million people in the United States suffer from GERD.

Acute failure of gastric motility and emptying is an almost inevitable event in critically ill or injured patients, even though small intestinal function is often well preserved.<sup>23</sup> The failure of gastric motility in this setting is a significant problem, as there is now convincing evidence that outcome in these patients is superior if nutritional needs are met by delivery of nutrients into the small intestine, rather than by parenteral nutrition.<sup>24</sup> The failure of gastric mechanical function, however, makes enteral feeding substantially more difficult.<sup>25</sup>

The driving force for gastric emptying is still controversial. There are three potential mechanisms determining the rate of gastric emptying: a) the pressure difference between intragastric and intraduodenal pressure during pyloric opening ("pressure pump" mechanism),<sup>4,5</sup> b) the intermittent increase in stomach pressure due to propulsive gastric contractions in the presence of relatively constant pyloric and duodenal resistance ("peristaltic pump" mechanism),<sup>4</sup> and c) the intermittent decrease in pyloric and duodenal resistance in the presence of a constant gastroduodenal pressure gradient ("pyloric resistance" mechanism).<sup>6</sup> The relative contribution of pressure pump, peristaltic pump and pyloric resistance to the gastric emptying process has been insufficiently delineated

in humans and almost solely investigated with invasive methods such as intraluminal manometry and gastric barostat. These techniques, however, do not provide data on emptying rates, intragastric meal distribution and stomach and gastric air volumes and therefore need to be combined with medical imaging techniques.<sup>4,7</sup>

The intragastric distribution of the meal volume between the proximal and distal stomach, as well as the distribution and mixing of single macronutrient (e.g., fat) within the meal, have a major impact on gastric function and satiety. The regulation of the underlying motility occurs via duodenal and small intestinal receptors initiating a feedback response. Motor mechanisms such as reduction in gastric tone,<sup>26</sup> suppression of antral pressure waves,<sup>27</sup> stimulation of tonic and phasic pyloric pressures,<sup>28</sup> and thus a reduction of transpyloric flow, are associated with the slowing of gastric emptying. Assessment and imaging of intragastric distribution and mixing are also important in pharmaceutical research for the development of orally administered drugs or drug delivery systems.<sup>29–33</sup> Here, the influence of the intragastric drug distribution and emptying on the effectiveness and bioavailability of drugs are of major interest. In this field, scintigraphy is the standard imaging method to assess and evaluate the *in vivo* performance of developed drug dosage forms,<sup>34,35</sup> but lacks the concurrent anatomical and functional information.

Over the last 10 years high performance clinical whole-body magnetic resonance imaging (MRI) systems became widely available. Continuous improvement of MRI gradient strength and speed (gradient fields and slew rates up to 40 mT/m and 200 mT/m/ms, respectively) together with dedicated coils allow rapid, high resolution and artefact free MRI data of the human abdomen and pelvis. Innovative sequencing and parallel imaging, a recently introduced new imaging method, show considerable potential to further increase imaging speed and/or image quality for MRI of organ function. Simultaneous development and application of various MRI contrast agents enabled significant improvements in image contrast and delineation of organs and vessels. These factors have improved the spatial resolution of MRI and brought acquisition speed into the physiological range of most GI events. Image acquisition in GI studies must be rapid because the bowel is in constant movement. Spatial resolution must be high to delineate thin walled, convoluted GI structures from other abdominal structures. These advances have stimulated investigation of MRI techniques for the study of GI function as well as structure and promise much for future applications in the clinic.

In recent years MRI was shown and evaluated to be a powerful medical imaging method for the measurement of gastric emptying, peristaltic activity, accommodation (tonic relaxation) and secretion<sup>15,16,36,37</sup> and the intragastric distribution of meal volume, macronutrient and specific MRI marker.<sup>19,38,39</sup> MRI also allowed the simultaneous assessment of all these parameters and thus provided new insights into gastric motor function in humans.<sup>40</sup> The flexibility in image acquisition, the capability for non-invasive, real-time and three-dimensional (3D) imaging with high image resolution, combined with the ability to detect tissue movement and luminal flow are factors that make MRI an almost 'ideal' method for the investigation of human gastrointestinal (GI) function.<sup>20</sup>

The thesis report starts with a review on the use of MRI for the assessment of GI function. This review, as described in chapter 1, intends to introduce the fundamental basics on GI physiology (and GI nomenclature) and highlight the motivation for this work

to the reader. Furthermore, it sets this research work in context to ongoing research on GI function.

The MRI studies performed in this work are divided into two main topics. The objective of the first group of studies, as described in chapter 2, was to introduce MRI as a valid and non-invasive tool for pharmaceutical research in humans, i.e. to develop MRI based methods for the monitoring and assessment of the *in vivo* performance of oral drug delivery systems. Detailed knowledge of the actual drug distribution (and emptying) in the post-prandial stomach is of paramount importance for controlling and improving the effectiveness and bioavailability of orally administered drugs. Aim of these studies was to assess the feasibility of two different MRI markers for tablet labelling and to study the intragastric position, residence time and movement of different orally administered tablets as well as the meal dependency of intragastric tablet performance (subsections 2.2.1, 2.2.2, 2.2.3). In addition, the effect of different meal viscosities and amounts of water ingested together with the meal on the intragastric distribution and mixing of a paramagnetic MRI marker (serving as a drug model) was analysed (section 2.1).

The objective of the second group of studies, as described in chapter 3, was to investigate human gastric motor function and emptying in different body position and after ingestion of different macronutrient. The studies simultaneously analysed important mechanical parameters of gastric function within one imaging session and aimed on improving and extending the understanding of the driving forces and the regulatory mechanisms of human gastric emptying. Furthermore, this work was motivated by the fact that modern high-field MRI systems have horizontally aligned whole-body architecture only allowing measurements of organ function in the lying body position. This presents a limitation for gastric MRI, since several studies have shown that posture influences gastric function.<sup>41–45</sup> Imaging protocols were developed for two MRI systems of different architecture (0.5 Tesla (T) open-configuration and 1.5 T whole-body MRI scanner) allowing assessment and intra-individual comparison of stomach and intragastric air volume, intragastric meal distribution, gastric emptying and gastric peristalsis between the seated (SP) and right decubitus (RP) body position and in particular also in the upside down position (UDP). Additionally, for the macronutrient study (section 3.3), a new gastric emptying model for an improved statistical analysis of the dynamics of gastric volume curves was developed. This three-parameter linear exponential gastric emptying model (LinExp) has the advantage of integrating initial increases in the volume curves, as it is often seen for nutrient liquids, whereas the standard gastric emptying model is limited to monotonically decreasing emptying curves. Applying the new analysis method to the MRI volume data allowed the determination of small differences in gastric volumes and emptying dynamics. The thesis report concludes with short individual discussions and conclusions on each described project followed by more general considerations on the advantages and limitation of applying MRI in GI research as well as in the clinical setting for the diagnosis of GI pathologies. As outlook, selected future research projects in the field of basic gastric physiology are outlined.

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# Chapter 1

## Review:

# Magnetic Resonance Imaging (MRI) for the Assessment of Gastrointestinal (GI) Function

Since the first successful nuclear magnetic resonance (NMR) experiments by Felix Bloch and Edward Purcell in 1946 and the first application of magnetic resonance for image production in 1973 by Paul C. Lauterbur, magnetic resonance imaging (MRI) has become an important medical imaging tool for medical research and in clinical practice. MRI is based on the principle of nuclear magnetic resonance (NMR), where protons are polarised inside a strong, static and very homogeneous magnetic field ( $B_0$ ). The resulting magnetization of the protons interact with radio frequency (RF) energy at a characteristic frequency (the Larmor frequency  $\omega_0 = \gamma B_0$  ( $\gamma$ , gyromagnetic ratio)) and thus can be excited with RF pulses using antennas or coils. After excitation, the protons themselves irradiate an electromagnetic field at frequency  $\omega_0$  and their NMR-signal can be detected using the same coils. For imaging, the protons of an object become spatially encoded applying magnetic gradient fields ( $G$ ) in all three directions in space ( $x$ ,  $y$ ,  $z$ ). During RF excitation,  $G_z$  is applied to select the thickness of the desired image plane, i.e. the resolution in  $z$ -direction (which by convention is vectored along the  $B_0$ -field). The in-plane resolution of the image is then attained by successive application of  $G_x$  and different  $G_y$ s until all data for image reconstruction are recorded. The technique is non-invasive and does not employ ionizing radiation; according to current understanding, no adverse implications of NMR or MRI on the human organism are known.

Although MRI is established in the clinical setting for the detection of anatomical structures and pathologies, it is not routinely employed for the investigation of organ function, e.g. cardiac contractility or GI motility. However, improvement of MRI gradient performance, innovative sequencing combined with parallel imaging techniques and also sophisticated MRI contrast agents enable the detailed visualisation of organ function and microcirculation in almost real-time. This dynamic imaging capability makes MRI the most promising medical imaging method in functional diagnostics.

In the following chapter, a short overview on current applications of MRI for assessing the function of the human gastrointestinal (GI) tract, with special reference to the stomach, is presented. Advantages of MRI for this purpose in relation to established medical

imaging tools and investigations are discussed. This should provide the reader with some rudimentary background on important GI physiology and GI nomenclature, highlight the motivation for this work and put the here presented research in context to on-going research on GI function.

## GI function assessed by MRI

In recent years it has been shown that MRI is a valid method for the measurement of gastric emptying, accommodation, secretion, motility and intragastric distribution of gastric contents. It has also been used to monitor intestinal and anorectal motility. The flexibility in image acquisition, the capability for non-invasive, real-time and three-dimensional (3D) imaging with high image resolution, combined with the ability to detect tissue movement and luminal flow are factors that make MRI an almost 'ideal' method for investigation of GI function.<sup>20</sup>

### Gastric emptying

Gastric emptying (GE) is an important determinant of GI transit that influences the digestion and absorption of ingested food. The rate of GE is highly variable, the outcome of a complex interaction between the structure and function of the stomach. The volume of the meal and its nutrient density have important effects on gastric physiology.<sup>46</sup> In addition, the mechanism of GE is affected by the physical and chemical properties of the meal<sup>37</sup> (e.g. solid vs. liquid, macronutrient composition), the intragastric distribution of gastric contents,<sup>18,41,47</sup> body movement<sup>48,49</sup> and position during emptying.<sup>43,44</sup> Despite this large volume of data, a universally accepted description of the physiology and control of GE has not been established. This is largely because of the limitations of the various techniques that have been applied to study gastric function. Unlike existing techniques, MRI can monitor several aspects of gastric function simultaneously under physiological conditions; this facility offers new possibilities to study the interaction and relative importance of the factors that determine GE.

Scintigraphy is the standard, non-invasive imaging method for the measurement of gastric emptying. For this investigation a test meal is labelled with radioactive isotopes and GE is measured by the fall in radioactivity in the gastric region detected by a gamma camera. Different radioactive isotopes are available for marking the solid and liquid components of a meal. GE was the first aspect of GI physiology to be assessed by MRI.<sup>14</sup> The MRI technique involves repeated acquisition of image stacks covering the gastric region after ingestion of the test meal. Multi-slice steady-state gradient echo imaging sequences (FFE or FISP) are applied due to their short acquisition times and good image contrast. Imaging is performed during breath holds to minimise movement artefacts. For analysis, the total gastric volume and meal volume are identified by distinct positive contrast and outlined on the MRI images. With positive paramagnetic contrast markers gastric volume can be corrected for gastric secretions by reference to the signal intensity of an external standard. The time plot of corrected gastric volumes provide a direct assessment of the half time ( $T_{50\%}$ , the time for the stomach to empty half of the meal) and the lag time ( $t_{lag}$ , the period after a meal before significant emptying begins) of the gastric emptying

process. The advantages of MRI over scintigraphy, include the lack of ionising radiation, no use of mathematical corrections based on phantom studies, the high spatial and temporal 3D image resolution, the simultaneous detection of total gastric volume (an indirect assessment of gastric tone (see below)), meal volume, and the surrounding abdominal anatomy. The flexibility of MRI in soft tissue contrast allows for accurate delineation of these volumes especially with the use of (side effect free) contrast agents.<sup>50</sup> MRI has been successfully validated against scintigraphy for liquid and mixed solid/liquid meals.<sup>15, 16, 50</sup> The results correlate closely for patients over a wide range of gastric emptying times in health and disease, including diabetic gastroparesis.<sup>51</sup> The technique is also sensitive to interventions that modulate the rate of gastric emptying.<sup>52, 53</sup>

## Gastric accommodation

Gastric accommodation describes the reduction in gastric tone and increase in compliance observed in the stomach following meal ingestion. It comprises two separate responses, receptive relaxation providing an appropriate reservoir for the ingested volume and adaptive relaxation co-determining the rate of gastric emptying. Gastric accommodation is important because reduced postprandial relaxation of the stomach is considered a likely cause of symptoms in non-ulcer dyspepsia<sup>54, 55</sup> and post-vagotomy syndromes. Conversely increased gastric accommodation might be a cause of gastro-oesophageal reflux.<sup>56</sup>

Gastric barostat techniques are the best established, albeit highly invasive, method for the assessment of gastric accommodation. This technique involves the introduction of a large compliant bag into the gastric fundus. The balloon is attached to a computer controlled pump that holds gastric pressure steady while monitoring changes in gastric volume over time. This technique allows post-prandial accommodation to be assessed in that a volume increase under isobaric conditions indicates gastric relaxation (and vice versa). Technical limitations of the technique are that it cannot be used with solid food and the presence of an intra-gastric balloon alters the motor response and intra-gastric distribution of the meal. Moreover the barostat is not sensitive to phasic contractions of the stomach (peristalsis). Non-invasive assessment of gastric accommodation is also possible with 3D reconstruction of ultrasound images using a position and orientation measurement device.<sup>57</sup> This significantly improves visualisation of the fundus compared to conventional two-dimensional (2D) techniques, however comparisons of 3D-ultrasound and barostat assessment of accommodation do not agree.<sup>58</sup> This may be due to measurement error or because different components of the accommodation response are measured by the different techniques.<sup>59</sup> Moreover solid meals cannot be studied by US because sonographic artefacts obscure the gastric dimensions.

MRI provides an (indirect) assessment of gastric tone by monitoring gastric volume change over time, using the imaging method described for gastric emptying. Further detail of the gastric tonic response can be obtained by dividing the stomach into proximal and distal stomach volumes. MRI measurements of gastric accommodation have been validated against gastric barostat. Although intra-gastric pressure is not controlled during MRI measurements, changes in barostat volume correlate accurately with MRI recordings during tonic pressure events after meal ingestion and tonic relaxation induced by glucagon.<sup>53</sup> A recent MRI study has investigated the effects of macronutrient composition on gastric accommodation after a meal in supine body position. The initial change in stomach and meal volume was identical as the stomach accommodated the volume load by re-

ceptive relaxation. During gastric emptying however, differential effects of macronutrient on gastric accommodation, peristalsis and emptying were observed, presumably reflecting adaptive effects on gastric physiology mediated by specific duodenal chemoreceptors.<sup>60</sup> A new MRI study was analysing for the first time the relationship between gastric emptying and volume responses after ingestion of liquids of different macronutrient composition (glucose, lipid, albumin), their magnitude and dependency on posture, as well as the their effect on gastrointestinal perception in healthy volunteers.<sup>61</sup> For all test meals, in both body positions, an initial increase in meal and stomach volume was observed. In seated position, gastric relaxation and initial change of meal volume was larger for glucose compared to fat and albumin, probably due to slowed initial emptying and accumulation of secretion. No difference was found for the lying position. Similar dynamics of meal and stomach volume as well as intragastric air volume were observed during emptying process in seated position for all three of macronutrient indicating that primarily, the ingested meal volume and, secondarily, its change by gastric secretion and emptying were the major determinants of gastric volume response. In right decubitus lying position, intragastric air volume increased over postprandial time, regardless of ingested macronutrient, leading to a larger stomach volume at a late emptying phase compared to sitting. The cause for this intragastric air increase (greater relaxation or retained air) could not be determined since no additional intraluminal pressure measurements were performed. Only small (and negligible) differences in the sensory responses for fullness, satiety and bloating for both body positions were found and all were possibly related to post gastric modulation of gastrointestinal sensations.

## Intragastric distribution

The intragastric distribution of the meal volume between proximal and distal stomach as well as the distribution of single macronutrient within the meal influence gastric function and satiety. For example the distribution of the fat component is of major interest, since the presence of fat in the small intestine strongly inhibits gastric emptying.<sup>62,63</sup> This regulation occurs via duodenal and small intestinal chemo-receptors that initiate a feedback response to ensure a steady supply of nutrients to the small bowel. This is achieved by mechanisms such as reduction in gastric tone,<sup>26</sup> suppression of antral pressure waves,<sup>27,64</sup> stimulation of tonic and phasic pyloric pressures<sup>65</sup> and thus a reduction of transpyloric flow. Existing techniques do not provide the spatial resolution required to monitor the distribution of gastric contents in the proximal and distal stomach, and only MRI can assess the various physiological responses that determine the distribution of the meal and the rate of GE.

MRI has been applied to determine the intragastric distribution, mixing and emptying of test meals of different viscosity and nutrient content.<sup>37,66</sup> Distal-to-proximal ratio of the meal volume was significantly influenced by nutrient content and viscosity. The impact of nutrient content to delay gastric emptying was stronger than that of viscosity, however distal gastric volumes and the sensation of fullness were increased with high-viscosity meals. Abnormal filling of the antrum have also been reported in patients with non-ulcer dyspepsia that experience postprandial fullness and discomfort.<sup>67,68</sup>

Another MRI study analysed an oil/water meal using chemical shift selective excitation enabling the imaging of lipid.<sup>18</sup> The resonant (Lamor) frequency of protons in fat is shifted with respect to those in water; thus the fat phase in the meal can be selectively

excited with specific narrow frequency-bandwidth RF pulses. Layering of fat separate to the aqueous phase was resolved. Depending on the body position during emptying (pylorus up or pylorus down) the fat layering emptied early or late leading to differential effects on gastric emptying, presumably because of the timing of feedback from duodenal receptors. In addition the mechanism of gastric emptying for liquid and solid meals was studied using T2 relaxation 'maps' that allow the assessment of the dilution of gastric contents with gastric secretions and the efficiency of the mixing/grinding process (trituration). In solid meals peripheral and more diluted components that are most exposed to the mechanical action of gastric contractile activity emptied more rapidly, suggesting an elution process.

Assessment and imaging of gastric function is also important in pharmaceutical research for the development of oral drug delivery systems. Here, the effects of the intragastric distribution and emptying on orally administered drugs are of major interest, since these factors can determine the effectiveness and bioavailability of the medication. In this field, scintigraphy is the standard imaging method to assess and evaluate the in vivo performance of developed drug dosage forms. Recently, MRI has been introduced to monitor the intragastric distribution of drug models within mixed solid/liquid meals in human volunteers.<sup>19,38</sup> These studies used a gadolinium (Gd) based positive paramagnetic contrast agent (Gd-DOTA (gadolinium 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate acid) to label a colloidal drug carrier (liposomes) or used the contrast agent itself as an aqueous drug model. Positive contrast agents shorten the  $T_1$  relaxation time of water protons in their vicinity that produces a stronger MRI signal and consequently increased signal intensity in the MRI image. Fast  $T_1$ -weighted gradient echo imaging sequences ( $T_1$ -FFE or FLASH) that produce a distinct contrast between liquids of different  $T_1$  relaxation times are used for image acquisition. The differentiation of drug model and normal meal is achieved by applying an appropriate signal intensity threshold during image analysis. Results showed that the intragastric distribution of the labelled liposomes and also the aqueous drug model depended substantially on the physicochemical characteristics of the ingested meal. This demonstrated that the effectiveness and bioavailability of an orally administered drug are strongly dependent on gastric function and meal composition. They may have substantial consequences, such as for enzyme preparations affecting fat digestion in chronic pancreatic insufficiency that rely on simultaneous arrival of enzymes and fat in the small intestines.<sup>69</sup>

The intragastric distribution of a drug also depends on the drug delivery system (e.g. tablets) that releases it. Gastric-retentive and controlled release systems have been developed to prolong the gastric residence time and dose the drug delivery to the systematic circulation. Gastric-retentive (floating) tablets of various density can be marked with either negative or positive paramagnetic contrast agents and monitored in vivo using MRI.<sup>33,70</sup> The intragastric position and release characteristics of the tablets was shown to be dependent on their density in relation to different meals.

## Gastric secretion

In the past, gastric secretion could only be investigated by invasive intubation techniques. These are unpleasant and may themselves influence the production of secretions, especially saliva.<sup>71</sup> By normalising the recorded meal signal intensity in the MRI image with a simultaneously recorded *ex vivo* reference signal the volume of gastric secretion can be

calculated using MRI.<sup>15,36</sup> There is an exponential correlation between the dilution of a labelled liquid meal and the signal intensity in the image. With solid meals a linear correlation is obtained.

Alternatively, Marciani et al.<sup>66</sup> measured gastric secretion via the reduction of meal viscosity due to dilution by mapping the transverse relaxation time ( $T_2$  relaxation time) of hydroxyl protons on polysaccharide molecules. The fast exchange of these protons with bulk water, determining the  $T_2$  relaxation of the solution depends on the polysaccharide entanglement, i.e. the viscosity. Thus the volume of gastric secretions, the dilution of gastric contents and the efficacy of the mixing/grinding process (trituration) can be calculated from changes in meal viscosity. In solid meals peripheral and more diluted components that are most exposed to the mechanical action of gastric contractile activity emptied more rapidly, suggesting an elution process.

Ongoing studies evaluate the approach of encoding the gastric dilution and mixing process into the longitudinal relaxation time ( $T_1$  relaxation time). The ingested meal is therefore marked with positive paramagnetic contrast agent. The concentration of the contrast agent within a given volume element and the corresponding  $T_1$  relaxation time show an exponential correlation. By repeatedly mapping the  $T_1$  relaxation times of the gastric content at normal image resolution local dilution processes due to secretion and mixing can be monitored and quantified.

## Gastric motility

Gastroduodenal motility exists in distinct fasting and postprandial states. In the fasting state powerful, occlusive gastroduodenal contractile activity (phase III of the migrating motor complex) clears the stomach of undigested debris. In the postprandial state peristaltic, often non-occlusive contractions migrate distally from the corpus to the antrum. When the contraction wave approaches the pylorus, the sphincter narrows forcing the gastric contents back into the body of the stomach. Together with chemical and enzymatic digestion, this process mixes and grinds solid matter into a somewhat homogeneous mixture (chyme) ready for passage through the pylorus into the small bowel.

Gastric ultrasound (US) has been applied to measure gastric motility in real time together with the assessment of flow using duplex Doppler US.<sup>72</sup> These techniques allow gastric US to reliably detect occlusive and non-occlusive peristaltic antral contractions and also transpyloric flow events.<sup>73</sup> However, the simultaneous measurement of gastric or meal volume is indirect and based on 2D measurements of gastric antral and/or fundic diameter.<sup>74</sup> This technique is user dependent and the images are often of poor quality and difficult to verify independently.<sup>75</sup> 3D reconstruction of US images to provide a volumetric assessment of total gastric volume is feasible,<sup>57</sup> but does not yet allow simultaneous acquisition of gastric peristalsis and other functional parameters.

Image planes positioned obliquely along the long axis of the stomach are used to assess gastric motility using MRI. On modern, clinical MRI scanners high-resolution, ultra-fast imaging of a single slice with a frame rate of 1–4 per second using dynamic steady-state free-precession imaging sequences (balanced FFE or TrueFISP) can be applied for image acquisition.<sup>76</sup> Alternatively, a bigger gastric area can be covered by acquiring a stack of three parallel image slices at a rate of one per second.<sup>40,77</sup> This time scale allows gastric contractions to be followed closely as they progress distally towards the pylorus. Analysis of the MRI images can quantify frequency, velocity and depth (occlusion) of gastric pres-

sure waves at pre-defined positions of the stomach. The motility imaging can be alternated with volume imaging of the total gastric region to simultaneously assess the rate of gastric emptying, gastric accommodation and the intragastric distribution. As with gastric US, MRI allows the detection of gastric flow events<sup>62</sup> and has been used to demonstrate that antral activity is associated with substantial forward and backward flow across the pylorus rather than simple, unidirectional peristaltic bolus transport. However, neither imaging methods has been able to acquire gastroduodenal flow profiles or volumes. The measurement of phasic gastroduodenal motility with MRI is more difficult than anatomical or volume studies for practical and technical reasons. Gastric shape and position can change with posture, respiration, and intrinsic muscular activity. Gastric contractions are not necessarily regular and high frequency and, in contrast to cardiac MRI, phase locking to GI myoelectrical events is not possible. Respiratory motion, small bowel activity, arterial blood flow in the aorta and the lateral and longitudinal movements of the contracting stomach impair MRI image quality especially in the antropyloroduodenal region.

The major limitation of MRI as well as US is that neither provides direct measurements of intraluminal pressure events. Manometry measures contractile activity in the stomach and small bowel, however both medical imaging tools were superior to manometry in detecting non-lumen-occluding contractions. For this reason both MRI and US have been combined with gastro-duodenal manometry.<sup>5,78</sup> Preliminary results suggest that gastric emptying of nutrient liquids occurs primarily during long episodes of relative antral quiescence, controlled by pyloric opening and possibly distal duodenal activity. This suggests that the gastro-duodenal pressure gradient rather than peristaltic mechanisms drive fluid emptying for nutrient liquids. Ongoing studies are combining volume, motility and velocity MRI sequences to provide unique insights into the mechanisms that control gastric emptying and together with intraluminal pressure readings a “global view” of gastric function.

## Pancreatic secretion

Magnetic resonance cholangiopancreatography (MRCP) shows promise as a replacement for diagnostic endoscopic retrograde cholangiopancreatography (ERCP), for example in the diagnosis of chronic pancreatitis<sup>79</sup> and cystic fibrosis.<sup>80</sup> The application of secretin stimulated MRCP (S-MRCP) improves imaging and delineation of the pancreatic duct and side branches and might help to detect early stages of chronic pancreatitis.<sup>81</sup> Furthermore, dynamic S-MRCP can determine the duodenal filling grade and thus allows the estimation of pancreatic exocrine function.<sup>82</sup>

Images are acquired using heavily  $T_2$ -weighted MRI sequences and depict the biliary tract, pancreatic duct and gallbladder as bright structures owing to the fluid within. Due to the long  $T_2$  and  $T_1$  relaxation times of bile and pancreatic fluids, rapid spin-echo imaging sequences such as turbo-spin-echo (TSE or RARE) and single-shot TSE (SSTSE or HASTE) are normally applied and show good reduction of motion artefacts.<sup>83,84</sup> These are combined with  $T_1$ -weighted fat-suppressed sequences to further improve delineation of intraluminal content. Image acquisition is achieved by single breath hold acquisition. 3D information can be generated from multi-slice, thin-slab TSE acquisition applying maximum-intensity-projection (MIP) algorithms and multiplanar reformatting techniques. Alternatively, a single-shot projection technique with a thick image slab of 30–70 mm can be acquired<sup>85</sup> allowing immediate image interpretation. Because of the morpho-

logical and functional properties and the complete non-invasive character of S-MRCP, it has the potential to become the first-line diagnostic modality in the near future. Still, further improvement of the quantitative assessment of exocrine function is required in order to get accurate functional and morphological pancreatic evaluation in a single diagnostic step.

## Intestinal motility

Postprandial motor function includes propulsive contractions and segmental contractions, serving both to move chyme forward and ensure effective contact of the absorptive mucosa with the luminal contents. As in the stomach, propulsive peristalsis is demonstrated only during phase III of the MMC. Imaging of intestinal function is technically difficult and usually restricted to the assessment of intestinal transit. MRI can observe transit, volume changes and contractions in the small bowel and colon, however quantitative assessment of bowel function is difficult because of unpredictable movement, the comparatively small diameter of the lumen, and the complex three-dimensional structure formed by the bowel. Nevertheless, the analysis of small gut function has been shown to be feasible. Distension of the small bowel can be produced by ingestion of ispaghula (Metamucil) in aqueous solution that forms a voluminous, non-absorbable, viscous hydrogel within the lumen.<sup>86</sup> Labelled with a positive paramagnetic contrast agent this enabled the measurement of not only small bowel anatomy but also contractility as assessed by dynamic  $T_1$ -weighted 2D gradient echo imaging (FFE or FISP) in prone position of small bowel diameter during breath holds. The sensitivity of the functional measurements has been demonstrated by pharmacological modulation.<sup>87</sup> Thus MRI provides not only an alternative to transit tests in the small bowel but also an opportunity to measure small bowel contractility. Modifications of the technique may permit the assessment of bolus transport through sections of the bowel.

## Defecography

Defecation involves the action of anorectal and pelvic floor muscles to evacuate stool from the rectum. The process involves the integrity of structural factors such as pelvic floor musculature and the coordinated function of voluntary and autonomic muscular function. A wide variety of complaints can be referred to damage, disease or abnormal function of defecation including chronic constipation, obstructed or incomplete evacuation, rectal prolapse and pelvic pain syndromes. Fluoroscopic defecography is a valuable technique in the diagnosis of anatomical changes during evacuation and anismus, however it is limited by poor visualisation of the pelvic floor and overlapping of structures and the comparatively high radiation dose required to image the pelvis.

With the advent of open configuration MRI systems, enabling the imaging in the upright sitting position, dynamic defecography has become possible. The rectum is filled with a semi-solid labelled with a positive contrast marker before the MRI measurement. A dynamic 2D gradient echo sequence recording sagittal MRI images is acquired during contraction of the pelvic floor and defecation. This technique provides a "global view" of pelvic viscera and musculature, permitting analyses of the anorectal angle, opening of the anal canal, functioning of the puborectal muscle, and descent of the pelvic floor during defecation. MRI has been validated against fluoroscopy with excellent agreement



for all variables.<sup>88,89</sup> Moreover, in a comparison of MRI defecography against standard clinical investigations, including proctography, a high level of agreement was detected. The clinical utility of MRI defecography is evidenced by the fact that it is the only MRI measurement of GI function that is routinely used in clinical practice.

## Conclusion

In summary, there is a large potential for the application of MRI techniques in the evaluation of GI physiology and a variety of motility disorders. The recent developments described in this review demonstrate the great flexibility of MRI in the field of gastrointestinal research. The technique combines many advantages of other medical imaging methods. It provides rapid image acquisition with excellent image quality, is non-invasive, reliable and does not expose the subject to harmful radiation. GI anatomy as well as function is visualised in the resting and postprandial state and intraluminal mixing and distribution processes can be monitored simultaneously. Nevertheless, more experience with these techniques must be gained in order to confirm the promise of this technique and to establish MRI in the clinical setting. In addition progress must be made in the automation of MRI image analysis, a process that is time consuming at present. If these issues are addressed, it could well be that MRI will replace existing investigations for the diagnosis and therapeutic monitoring of gastrointestinal motility disorders.

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## Chapter 2

### Magnetic Resonance Imaging in pharmacological research:

### MRI for monitoring and evaluating intragastric drug distribution and oral drug delivery systems

#### 2.1 Effects of meal consistency and ingested fluid volume on the intragastric distribution of a drug model in humans - an MRI study

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## Abstract

**Background:** Controlled delivery of drugs to the small intestine in relation to emptying of the ingested meal is important in various pathophysiological conditions. We investigated the effects of different food consistencies and the amount of co-ingested liquid on the intragastric distribution of a contrast marker. **Methods:** Five healthy subjects received four meals (each 650 kcal: A, mashed potato with 100 ml water; B, rice with 100 ml water, respectively; C, hamburger meal with 100 ml water; D, hamburger with 300 ml water). A capsule filled with gadolinium tetra-azacyclododecane tetra-acetic acid solution (as contrast marker) was ingested following meal termination, and its intragastric distribution was assessed by magnetic resonance imaging. **Results:** Initially, marker distribution was confined to the fundus, and subsequently extended along the inner curvature of the stomach. The maximum distribution volume of the marker was lower in meal A than in meal B ( $P < 0.05$ ). No differences in marker distribution were observed when the hamburger meal was given with 100 or 300 ml water. **Conclusions:** Intragastric distribution kinetics of the marker gadolinium tetra-azacyclododecane tetra-acetic acid appeared to depend on meal consistency, but not on the amount of water co-ingested. Three-dimensional magnetic resonance imaging allows detailed analysis of the intragastric distribution of a drug model in relation to meal emptying and intragastric meal distribution.

**Key words:** intragastric drug distribution; contrast agent; magnetic resonance imaging.

## Introduction

Knowledge of the fate of an orally administered drug in the gastrointestinal tract may be of crucial importance for the development of drugs. For example, orally administered enzyme preparations aiming to improve fat digestion and, consequently to control steatorrhea in chronic exocrine pancreatic insufficiency, are often not distributed homogeneously within the gastric content. Therefore, they do not empty simultaneously with the food into the small intestine, diminishing their efficacy to improve maldigestion.<sup>90-92</sup>

Among the various techniques used to study release and distribution of orally administered drugs *in vivo*, scintigraphy has been most successful in visualizing the fate of pharmaceutical dosage forms in the gastrointestinal tract.<sup>32,93</sup> However, when detailed knowledge on the location of drug-food interactions or of the properties of complex release systems is sought, the two-dimensional nature of scintigraphy imposes limitations that can be overcome by the three-dimensional (3D) capabilities of magnetic resonance imaging (MRI). We recently used MRI to follow the intragastric release of a colloidal drug model containing gadolinium tetra-azacyclododecane tetra-acetic acid (*Gd*-DOTA) from a gelatine capsule in the food filled human stomach.<sup>19</sup> We observed that distribution of the drug model in the stomach (i.e. within the meal) was dependent on the composition and consistency of the meal. The drug model appeared to distribute predominantly in the accessible liquid compartment of the meals. Our data also suggested that the degree of homogeneity of the drug model distribution in the stomach may influence the time course of drug release into the small intestine (i.e. gastric emptying).

The first aim of the present study was to investigate the effects of test meals of different consistencies and containing different amounts of liquid ingested with the meal on the intragastric distribution of a contrast marker. This was achieved by administering a gelatine capsule containing *Gd*-DOTA solution, an MRI contrast agent, and visualising its release

from the capsule after ingestion of meals of different composition. The second aim was to demonstrate the 3D capabilities of MRI in clarifying the distribution processes in the stomach. We hypothesised that the intragastric distribution of a marker will be related to the amount of accessible liquid contained in the meal, and that the consistency of the meal will affect the spatial distribution of the contrast marker in the stomach, resulting in large differences in the timing of its delivery to the small intestine.

## Methods

### Subjects

Five healthy male subjects, aged between 22 and 30 years, participated in the study. The subjects were of normal weight for height (BMI:  $22.7 \pm 0.9$  kg/m<sup>2</sup>), had not taken any medication prior to or during the study and had no history of gastrointestinal disease. The study was carried out with the approval of the Ethics Committee at the University Hospital Zurich. All subjects gave their informed written consent prior to participation.

### Study design

The intragastric distribution of the MRI contrast agent *Gd*-DOTA (Dotarem®, Laboratoire Guerbet, Aulnay-sous Bois, France), administered in a hard gelatine capsule (see below for details), was examined after ingestion of four test meals differing with regards to their consistency and the amount of water co-ingested, but equal in energy and fat content (see table 2.1 for the composition of test meals). The study was divided in two parts: in the first part, we used a homogeneous meal (A) and a particulate meal (B) to assess the influence of different meal consistencies on the intragastric distribution of the contrast marker. In the second part, we examined the effect of different amounts of water ingested with a hamburger meal on the distribution of the contrast marker (meals C and D). This meal was chosen because it more closely resembles a ‘normal’ mixed meal.

### Magnetic resonance imaging (MRI)

The MRI investigations were performed with a commercial 1.5 T MRI system (Gyrosan ACS-NT, Philips Medical Systems, Best, NL). After the subjects were positioned in the MRI system, sets of 20 parallel images of the gastric region were acquired at regular time intervals (turbo spin echo technique, TR/TE = 500/9ms, 256<sup>2</sup> matrix). The spatial resolution was 1.7 mm × 1.7 mm × 8 mm, and each image set was acquired in 20 s. In each image, the outline of gastric content was determined in a semiautomatic procedure based on the anatomical structures visible in the images. This yielded all volume elements (voxels) of gastric content, which were then analysed based on their signal intensity. The contrast agent *Gd*-DOTA led to a local increase in signal intensity by affecting the protons in its vicinity. To differentiate between gastric regions containing *Gd*-DOTA and those not containing the contrast agent (background), a threshold signal intensity was chosen based on the intensity distribution of the voxels in the gastric content in a scan taken prior to capsule administration (reference scan). Each voxel with an intensity above the highest intensity in the reference scan was then assumed to be a volume element containing *Gd*-DOTA. The image intensity was standardized between images and over the course of the study by referencing all images to the signal intensity of an external control.

Meal	Meal composition	Meal weight	Macronutrient composition	Energy content
<b>A</b>	<b>300 g mashed potato</b> 45 g butter 100 ml water	445 g	37% fat 7% protein 56% carbohydrates	636 kcal
<b>B</b>	<b>300 g rice</b> 45 g butter 100 ml water	445 g	33% fat 5% protein 62% carbohydrates	657 kcal
<b>C</b>	<b>100 g hamburger</b> 120 g green beans 100 g French fries 10 g herb butter <b>100 ml water</b>	430 g	36% fat 31% protein 33% carbohydrates	650 kcal
<b>D</b>	<b>100 g hamburger</b> 120 g green beans 100 g French fries 10 g herb butter <b>100 ml + 200 ml water</b>	430 g	36% fat 31% protein 33% carbohydrates	650 kcal

Table 2.1: Composition of the test meals

### Preparation of *Gd*-DOTA containing capsules

An aqueous solution of the MRI contrast agent *Gd*-DOTA served as a contrast marker. 500  $\mu$ l *Gd*-DOTA solution (0.5 mM/ml) was administered to the subjects in a double capsule (to increase the time before release in the stomach) consisting of a transparent, closed and sealed hard gelatine capsule (size 1; nominal volume, 500  $\mu$ l) inside a hydroxypropylmethylcellulose (HPMC) capsule (size 0; nominal volume, 680  $\mu$ l). After sealing of the injection hole, the capsule was immediately given to the subjects positioned in the MRI system. Although the encapsulated *Gd*-DOTA solution does not truly resemble a drug, it allows, at least in principle, the investigation of the intragastric distribution of an aqueous preparation relative to the meal with which it was ingested.

### Examination protocol

The subjects were allowed a light breakfast before 08.00 hours, but no food or drink except water thereafter, and arrived at the MRI centre in the early afternoon (after 13.00 hours). Each subject received, on four different days and in randomised order, one of the four test meals described in detail in Table 2.1. The butter used in meals A and B was thoroughly mixed into the mashed potato or rice prior to ingestion and was added to match the fat content of the hamburger meals C and D. The water was consumed with the meal. Immediately after meal ingestion, subjects were positioned in the MRI system in a supine, 30°right tilted position, and a reference scan was performed to map the signal intensity of gastric content. Then, the *Gd*-DOTA-filled capsule was administered to the subjects. Opening of the capsule and, subsequently, the dynamic distribution of the contrast marker was followed over 60 min. MRI scans were performed continuously until release of the marker from the capsule was first observed (time  $t = 0$  min), and thereafter every 5 min

until  $t = 20$  min, then at  $t = 30$  min, 45 min and 60 min.

The construction of the MRI system necessitates investigations with the subjects in supine position. Since this is not ideal for gastric emptying studies, as it potentially forces the fundus (proximal stomach) in a more dependent position relative to the antrum (distal stomach), we adjusted the position of the subjects by turning them into a (supported) 30° right tilted position. In this way, the redistribution of food from proximal to distal stomach was possible, as is the case during 'normal' gastric emptying.

## Data analysis

*Gastric meal emptying.* The gastric content was outlined in each image in all 20 slices to obtain the gastric volume at each time interval.<sup>14</sup> Gastric emptying was expressed as the percentage of gastric content remaining at  $t = 60$  min.

*Distribution of the contrast marker.* The contrast marker was differentiated from the background intensity in the stomach by using the highest intensity found in the reference scans as a threshold value for subsequent analysis. Marker distribution was calculated for the whole stomach and for fundic and antral sub-regions, and was expressed as absolute (ml), maximum and relative distribution volumes. The maximum distribution volume of the marker described the greatest volume occupied by the marker during the study relative to the total volume, expressed as a percentage. The relative distribution volume was defined as the number of volume elements above the threshold value (as defined above) divided by the volume of the respective gastric region, expressed as a percentage. For the calculation of the distribution volumes of the whole stomach, all voxels within the gastric content were analysed for their signal intensities. Gastric sub-regions were identified from coronal projections of the stomach. The gastric incisure as an anatomical landmark was used to define the partition of the stomach in the fundus and antrum. For analysis, two anatomical axes were defined that were aligned with the long axis of the fundus or antrum, respectively. All subsequent calculations were done based on these two axes. To analyse the distribution volumes of the two sub-regions, the fundus and antrum, the volume elements (voxels) in gastric content were accumulated in partitions orthogonal to the defined axes and analysed for their signal intensities. Joining these two axes resulted in a residual volume at the non-continuous transition (Figure 2.1(a)). Due to our primary interest in the distribution processes in the proximal and distal stomach regions, the absolute, maximum and relative distribution volumes were analysed for the fundus and antrum only.

*Visualisation of distribution.* The stomach surface, meal volumes and distribution of the contrast marker were visualized using a software package for the development of interactive 3D graphics applications (OpenGL Inventor, SGI, Mountain View, CA, USA).

*Statistical analysis.* Data are expressed as medians (interquartile ranges). The Wilcoxon rank test was used to test for statistical significance. For multiple testing, Friedman analysis of variance was used.  $P < 0.05$  was regarded as significant.

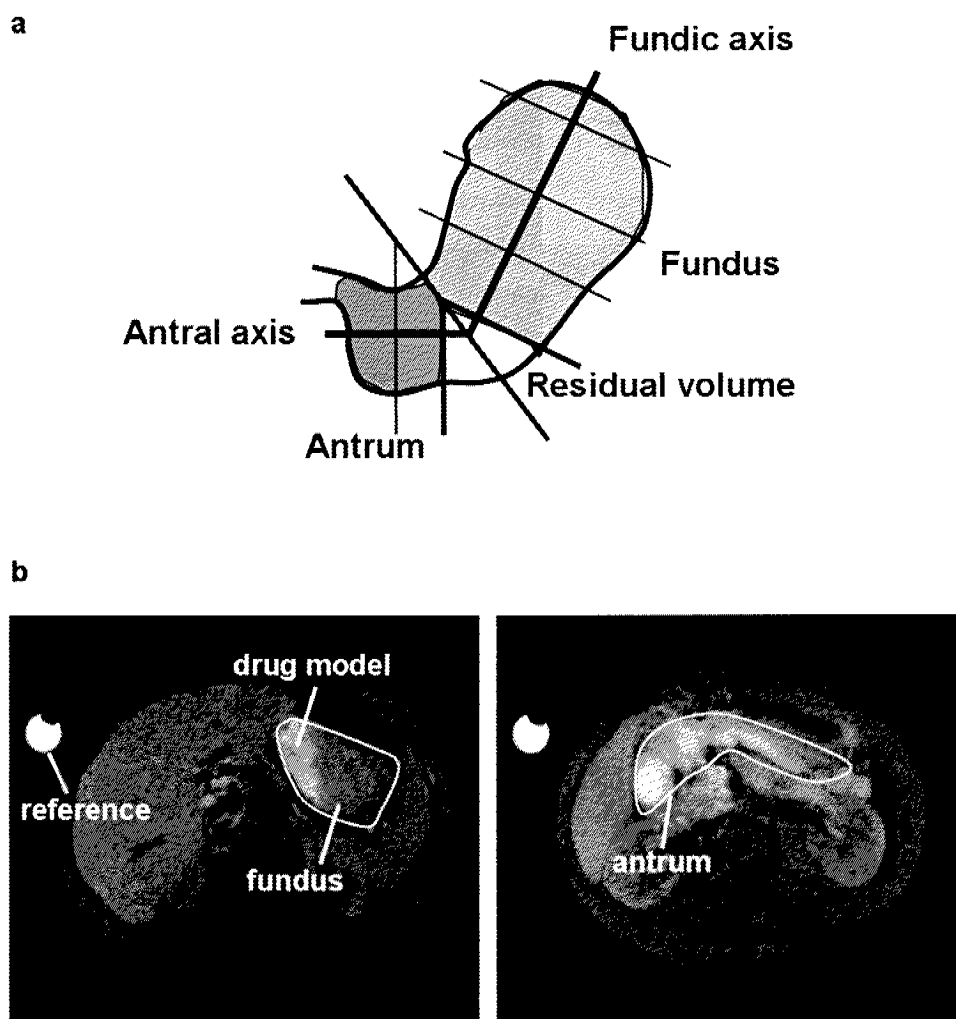


Figure 2.1: (a) Sketch of coronal view of the stomach with outlined fundic and antral axes that were used for analysis. (b) MRI images (transversal cross-sections) of the food-filled stomach acquired 20 min after release of the marker from the capsule. The marker can be distinguished as a bright signal against the meal. Distribution in this situation (meal B) was rather homogeneous in the antrum, while only a small proportion of the meal in the fundus was mixed with the marker.



Marker			
volume	total stomach	fundus	antrum
<i>meal A</i>	72 (70–127)	21 (8–35)	37 (13–64)
<i>meal B</i>	198 (154–202)	93 (47–94)	79 (70–98)
<i>meal C</i>	113 (66–133)	30 (26–45)	52 (24–85)
<i>meal D</i>	138 (62–149)	38 (6–54)	82 (59–89)

Meal			
volume	total stomach	fundus	antrum
<i>meal A</i>	413 (377–435)	209 (203–226)	115 (73–116)
<i>meal B</i>	486 (438–487)	278 (190–290)	106 (104–107)
<i>meal C</i>	422 (409–480)	229 (213–250)	87 (79–93)
<i>meal D</i>	434 (423–471)	202 (194–224)	133 (107–146)

Data are given in [ml] and expressed as median (interquartile ranges)

Table 2.2: Absolute maximum distribution volume of marker [ml] and absolute meal volume [ml] for the entire gastric lumen, fundus and antrum.

## Results

### Effect of different meal consistencies on contrast marker distribution

We used a homogeneous meal (meal A) and a particulate meal (meal B) to study the effect of different meal consistencies on the intragastric distribution of a contrast marker. The MRI images in Figure 2.1(b) show the intragastric distribution of the marker volume at 20 min after release from the capsule in meal B. The maximum distribution volume of the marker in the entire stomach was lower in meal A than in meal B (meal A: 23% (22–37%); meal B: 49% (45–65%);  $P = 0.043$ ). In the fundus, no differences were found between the two meals (meal A: 11% (3–15%); meal B: 34% (13–49%);  $P = 0.138$ , n.s.). In the antrum, maximum distribution volume of the marker was lower in meal A than in meal B (meal A: 51% (42–55%); meal B: 72% (72–83%);  $P = 0.043$ ). The distribution (relative volumes) of the marker over the course of the study is shown in Figure 2.2 for meals A and B. The characteristics of the spatial distribution of meals A and B are illustrated in the 3D images at  $t = 45$  min after capsule opening (Figure 2.3) and in the distribution volume at two time points for meal B (Figure 2.4). This example illustrates that the distribution from the capsule commenced in the fundus and extended along the inner curvature of the stomach in both meals. However, in meal A, the marker did not significantly distribute in the antrum. This is further illustrated by Table 2.2, Which gives an overview of the absolute distribution volumes of the marker and meal volumes in the total stomach and in the fundic and antral subregions. The data show that the meal volume in the fundus amounts to approximately twice the volume in the antrum, while the marker is distributed evenly between antrum and fundus.

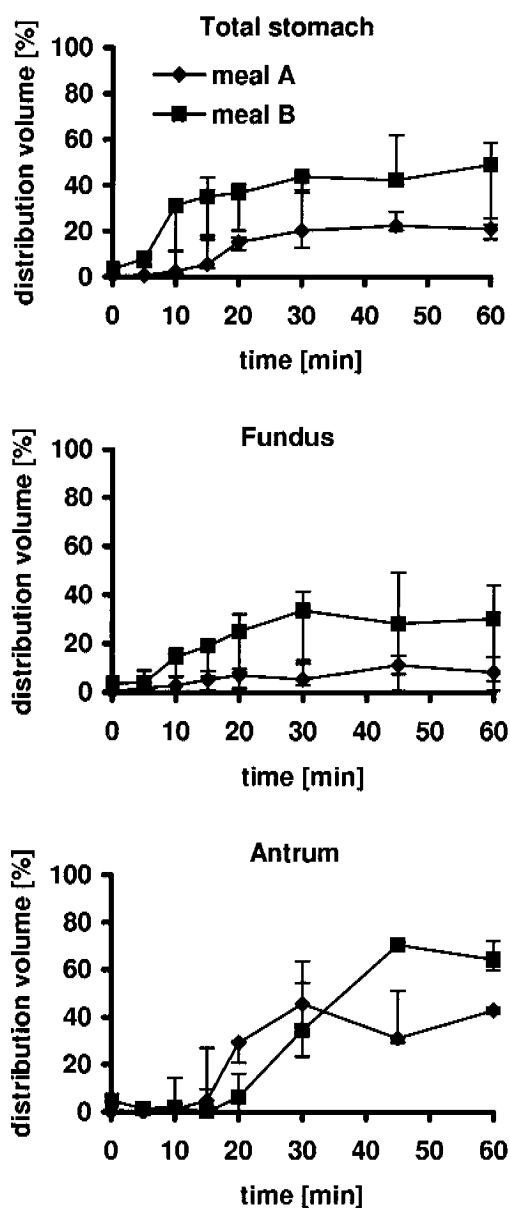
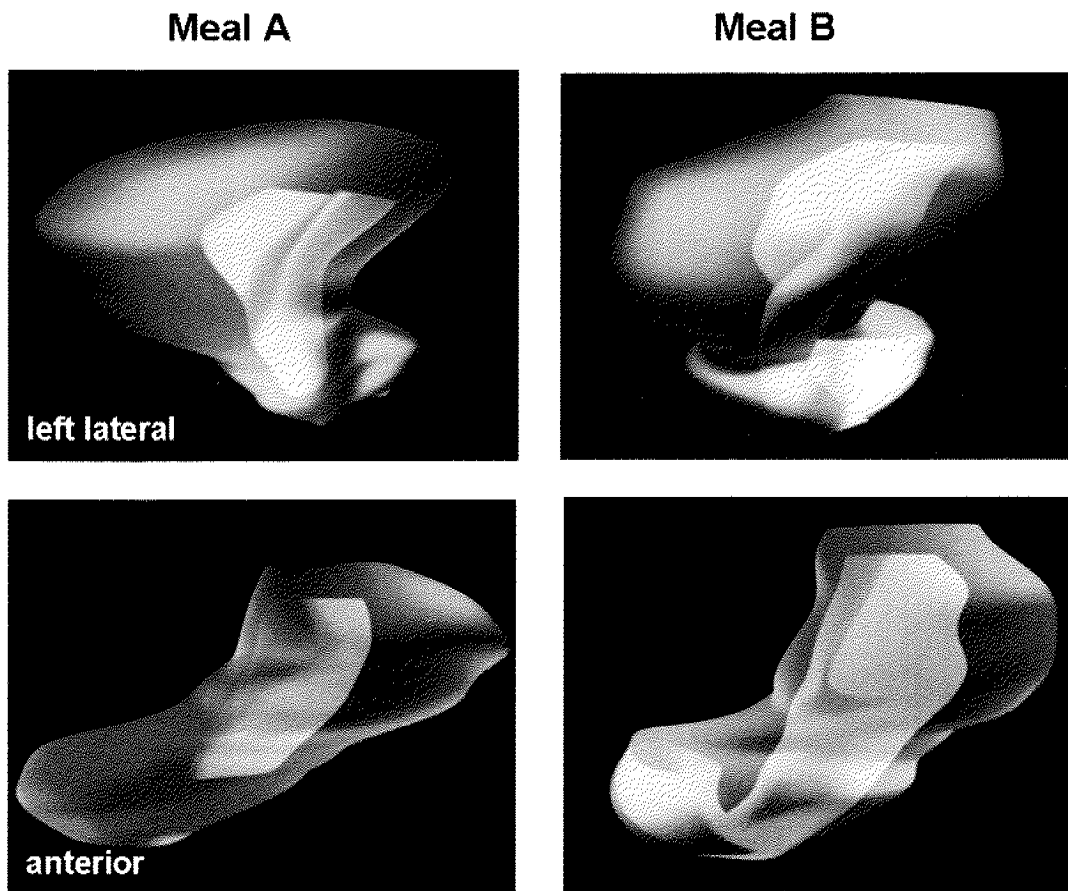
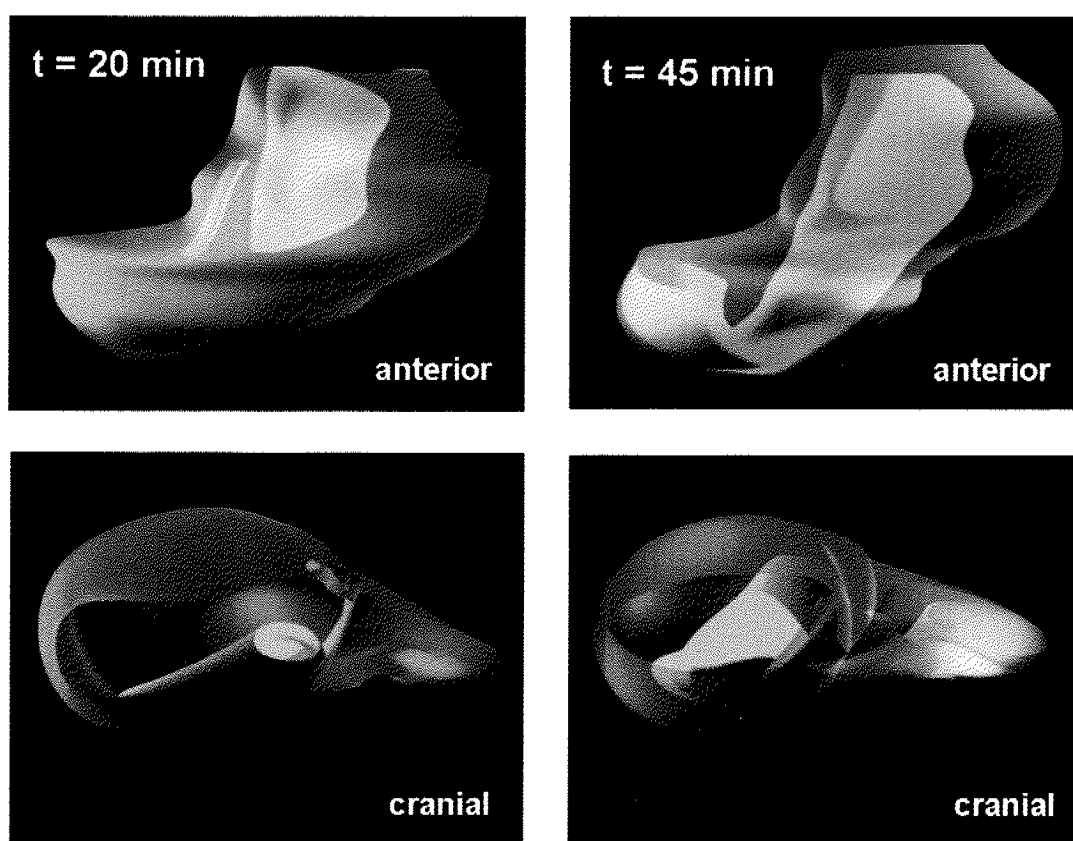


Figure 2.2: Distribution of the marker over the course of the study for meals A (♦) and B (■) for the total stomach, fundus and antrum. While maximum distribution volume of the marker in the entire stomach and antrum was lower in meal A than in meal B, no significant differences were found in the fundus. Data are expressed as medians (interquartile ranges).



*Figure 2.3: 3D reconstruction of the gastric region for meal A (left) and meal B (right) at 45 min after release of the marker (red). The meal is shown in blue. At this time, the marker had already distributed in the fundus and antrum in meal B, while distribution was still confined to the fundus in meal A.*



*Figure 2.4: Comparison of two time points, 20 and 45 min after marker release, for meal B. Distribution started in the fundus and occurred along the inner curvature into the antrum.*

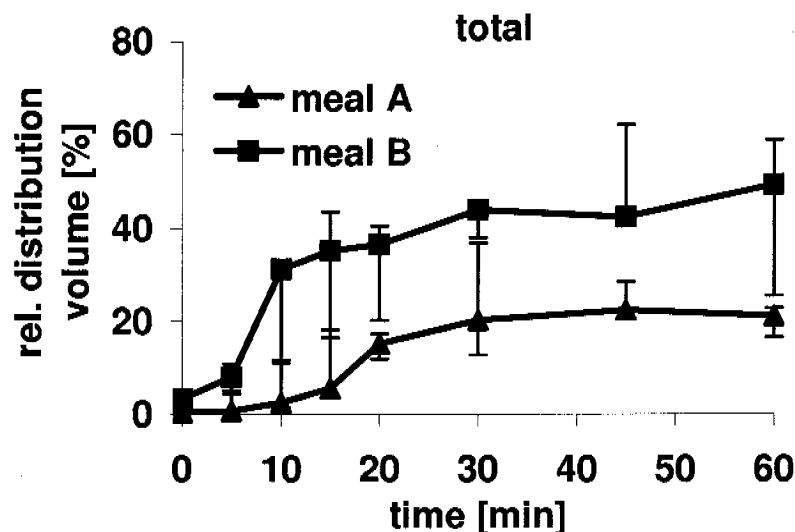


Figure 2.5: Comparison of two time points, 20 and 45 min after marker release, for meal B. Distribution started in the fundus and occurred along the inner curvature into the antrum..

### Effect of ingested liquid

The effect of the amount of water ingested with the meal on the intragastric marker distribution was analysed in the two hamburger meals with 100 or 300 ml water (meals C and D, respectively). No differences in the maximum distribution volume of the marker were observed between the two meals for any of the gastric regions (total stomach: meal C, 28% (25–31%); meal D, 34% (25–40%);  $P = 0.500$ , n.s.; fundus: meal C, 20% (8–47%); meal D, 13% (4–28%);  $P = 0.345$ , n.s.; antrum: meal C, 30% (22–66%); meal D, 59% (50–64%);  $P = 0.686$ , n.s.). The relative distribution volumes of the marker between the two meals did not differ over the course of the study (Figure 2.5). The assessment of the absolute distribution of the marker and the meals in the different gastric regions (Table 2.2) indicated that a greater proportion of the meal (at the beginning of the study) was present in the fundus and only a small proportion (approximately a quarter of the meal) was in the antrum. On the other hand, after release from the capsule, the contrast marker distributed into a greater meal volume in the antrum than in the fundus.

### Gastric emptying

Gastric emptying during the study was not significantly different between any of the meals (meal A, 63% (60–67%); meal B, 74% (73–91%); meal C, 75% (68–84%); meal D: 71% (66–81%);  $P = 0.178$ , n.s.).

### Discussion

In this study, we have shown that meal consistency can strongly affect intragastric distribution of a contrast marker after the ingestion of meals with similar gastric emptying

rates. On the other hand, the amount of liquid ingested with the meal has only a small effect on intragastric marker distribution.

We observed significant differences in contrast marker distribution between meals A (homogeneous) and B (particulate). Generally, in the antrum, meal and contrast marker were mixed more homogeneously, while a large part of the meal in the fundus was not accessible to the marker. This may indicate, that under certain circumstances, a drug may be emptied from the stomach before the meal, even when the capsule is ingested after the food, or when given in a liquid form. The differences in intragastric marker distribution between the rice (particulate) and the mashed potato (homogeneous) meals may perhaps be explained by the different meal consistencies. The particulate nature of the rice meal made the meal more easily accessible to the liquid, while the mashed potato meal with its denser consistency, could only be infiltrated by liquid, and hence the marker, to a limited extent. This interpretation is also in line with our hypothesis that intragastric distribution of a contrast marker is related to the accessible liquid volume.<sup>19</sup> We tested this hypothesis further by administering to our subjects two meals that varied only in the amounts of water ingested. Accordingly, the contrast marker should have distributed in a larger volume in meal D, containing 200 ml more water than meal C. However, the distribution volumes did not differ between the two meals. One explanation may be the rapid gastric emptying rate of non-nutrient liquid,<sup>94</sup> preventing a homogeneous distribution of the marker in the liquid phase over the course of the study. A nutrient-containing drink, as used in our previous study,<sup>19</sup> may have provided different results, as it is emptied from the stomach more slowly and may therefore allow more time for the distribution process to occur.

For all meals, the contrast marker showed a preferential distribution from the fundus along the inner curvature of the stomach wall into the antrum. Consequently, a large proportion of the fundic content did not come into contact with the marker. According to our results, it is likely that the marker bypassed a large part of the meal, in particular in the fundus, and was emptied from the stomach before any significant mixing with the meal had taken place.

Our data show that MRI is a valuable technique to study the behaviour of oral dosage forms, as 3D gastric images can be reconstructed and important parameters, such as gastric emptying and motility, can be monitored.<sup>19,95,96</sup> Also, MRI allows performance of repeated studies in healthy subjects, since it does not involve exposure to ionising radiation. It is important to note that our studies have focused on the assessment of the intragastric distribution of the marker rather than on small intestinal exposure to the marker. As our calculations of marker concentrations are based on measured intensities, very small concentrations, such as those emptied into the small intestine, may, at this stage, fall below the detection limit. Also, MRI allows the performance of repeated studies in healthy subjects, as it does not involve exposure to ionizing radiation. A variety of techniques have been used previously to study the fate of pharmaceutical dosage forms. The most commonly used method for *in vivo* imaging to date has been  $\gamma$ -scintigraphy.<sup>32</sup> Dual-isotope imaging techniques allow labelling of drug and meal, and thus the assessment of drug distribution relative to the meal.<sup>92,97</sup> This is an advantage over MRI, where direct labelling of the drugs with an MRI marker has so far not been approved for clinical studies. Significant limitations of  $\gamma$ -scintigraphy include the restriction to two dimensions and the exposure to ionizing radiation. As alternative methods, gastrointestinal magnetomarkergraphy and a superconducting quantum interference device (SQUID) have been

proposed to study transit times through the gastrointestinal tract.<sup>98,99</sup> However, studies utilizing these methods only focus on the location of solid, non-disintegrating capsules and do not provide information on the release of a dosage form.

Our data indicate that meals with a similar energy content empty from the stomach at similar rates regardless of their composition and consistency. Meals with a more particulate consistency (rice, hamburger meal) probably mixed reasonably well with gastric secretions and ingested liquid, were ground and then emptied. The homogeneous meal (mashed potato) did not require trituration, but emptied from the stomach at a similar rate. This may be due to the denser consistency of this meal, resulting in a longer period of time for gastric secretions to penetrate and liquefy this meal. The results are in agreement with earlier studies showing that meal consistency only had a modest influence on gastric emptying.<sup>100,101</sup>

In summary, our data show that meal consistency has a significant impact on the intragastric distribution of a contrast marker, even at similar gastric emptying rates of the meals. Furthermore, our data indicate that non-nutrient fluid ingested with the meal does not appear to increase the intragastric distribution of the marker. We also demonstrated that MRI can simultaneously visualize distribution kinetics of the marker in relation to gastric anatomy in three dimensions and at high resolution. This technique will therefore be of great value for optimizing the behaviour of new dosage forms and for the analysis and clarification of basic distribution mechanisms in the stomach.

## Acknowledgment

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## 2.2 MRI for the evaluation of gastric-retentive tablets in humans

### 2.2.1 Magnetic Resonance Imaging for the *in vivo* evaluation of gastric-retentive tablets

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## Abstract

**Purpose.** To develop a magnetic resonance imaging (MRI) technique for assessing *in vivo* properties of orally ingested gastric-retentive tablets under physiological conditions.

**Methods.** Tablets with different floating characteristics (tablet *A* – *C*) were marked with superparamagnetic  $Fe_3O_4$  particles to analyze intragastric tablet position and residence time in human volunteers. Optimal  $Fe_3O_4$  concentration was determined *in vitro*. Intragastric release characteristic of one slow-release tablet (tablet *D*) was analyzed by embedding gadolinium tetra-azacyclododecane tetra-acetic acid chelates (*Gd*-DOTA) as a drug model into the tablet. All volunteers underwent MRI in the sitting position. Tablet performance was analyzed in terms of relative position of tablet to intragastric meal level (with 100% at meal surface), intragastric residence time (min) and *Gd*-DOTA distribution volume (% of meal volume).

**Results.** Intragastric tablet floating performance and residence time of tablets (tablet *A* – *D*) as well as the intragastric *Gd*-DOTA distribution of tablet *D* could be monitored using MRI. Tablet floating performance was different between the tablets (*A*, 93% (95–9%); *B*, 80% (80–68%); *C*, 38% (63–32%);  $P < 0.05$ ). The intragastric distribution volume of *Gd*-DOTA was 19.9% proximally and 35.5% distally.

**Conclusions.** The use of MRI allows the assessment of galenic properties of orally ingested tablets in humans in seated position.

**Key words:** human stomach; drug delivery systems; floating tablet; superparamagnetic contrast marker; *Gd*-DOTA; intragastric tablet performance; seated magnetic resonance imaging.

## Introduction

The gastrointestinal tract is still the preferred site for the delivery of therapeutic agents to the human body. Gastric-retentive oral dosage forms designed to prolong gastric residence time and to control drug delivery have gained increasing interest.<sup>29,31</sup> By combining prolonged gastric residence time and controlled release characteristics gastric-retentive drug delivery systems improve the bioavailability of drugs and may lead to a reduction of drug toxicity by avoiding uncontrolled plasma peak concentrations.<sup>102,103</sup>

The assessment of the *in vivo* performance is important for any pharmaceutical dosage form when designing a new drug, especially in case of gastric-retentive drug formulations. So far,  $\gamma$ -scintigraphy is the most widely used technique for this purpose. The technique is based on radiolabeling the drug dosage form under investigation, which can be monitored subsequently over time.<sup>32,34</sup> The main drawbacks of  $\gamma$ -scintigraphy are the associated ionizing irradiation for the patient, the limited topographic information and low resolution inherent to the technique and the complicated and expensive preparation of radiopharmaceuticals.

In the last couple of years, magnetic resonance imaging (MRI) was shown by our group<sup>15,16,19,38,50</sup> and others<sup>18,37,62,66,104</sup> to be a novel, valuable tool in gastrointestinal research for the analysis of gastric emptying, motility, and intragastric distribution of macronutrient and drug models. The use of MRI in studying oral drug delivery is limited so far, although the inherent advantages of MR imaging are potentially very favorable for this purpose. These advantages include high soft tissue contrast, high temporal and spatial resolution, as well as the lack of ionizing irradiation. Also, harmless paramagnetic and

superparamagnetic MRI imaging contrast agents can be applied to specifically enhance or suppress signals of fluids and tissues of interest and thus permit better delineation and study of organs.

The purpose of this study is to develop and implement an MRI technique that allows the assessment of the *in vivo* performance of ingested slow-release gastric-retentive tablets in asymptomatic volunteers. Volunteers were investigated in the seated position using an open-configuration MRI system. Therefore, gastric-retentive tablets were labeled with superparamagnetic iron oxide ( $Fe_3O_4$ ) particles as tablet marker or were loaded with paramagnetic gadolinium (*Gd*) chelates (*Gd*-DOTA) as drug model to enable *in vivo* monitoring of tablets with MRI.

## Methods

An initial *in vitro* study was conducted to evaluate the use of superparamagnetic  $Fe_3O_4$  particles as tablet marker in MRI. Furthermore, a pulverized form of the paramagnetic gadolinium tetra-azacyclododecane tetra-acetic acid (*Gd*-DOTA) solution was prepared to be embedded into the matrix of a slow-release floating tablet and to serve as water soluble model drug.

In the following *in vivo* study,  $Fe_3O_4$  marked floating tablets of different density were prepared and analyzed for intragastric position in the human food-filled stomach. The drug model release and distribution from a slow-release floating tablet containing *Gd*-DOTA were also investigated in human volunteers.

### Preparations and *in vitro* studies

#### *Fe<sub>3</sub>O<sub>4</sub> as tablet marker*

A gastric-retentive floating tablet was marked with different concentrations of  $Fe_3O_4$  (i.e. 0 %, 0.05 %, 0.1 %, 0.5%, 1 %  $Fe_3O_4$ ) in house at the pharmacy of the University Hospital to determine optimal  $Fe_3O_4$  concentration for tablet labeling. The tablets were imaged in water at pH 4.5 and 37 °C using a 0.5 T open-configuration MRI system (Signa SP, General Electric Medical Systems, Milwaukee, WI). Sequence parameter were chosen to resemble the *in vivo* situation ( $T_1$ -weighted fast spoiled gradient echo (FSPGR) technique; 30 sagittal image slices; repetition time ms/echo time ms 150/8; field of view, 280 mm; flip angle, 60°; matrix, 256 × 160; slice thickness, 8 mm; interslice gap, 0 mm). Images were acquired at 30 min intervals for at most 4 hours.

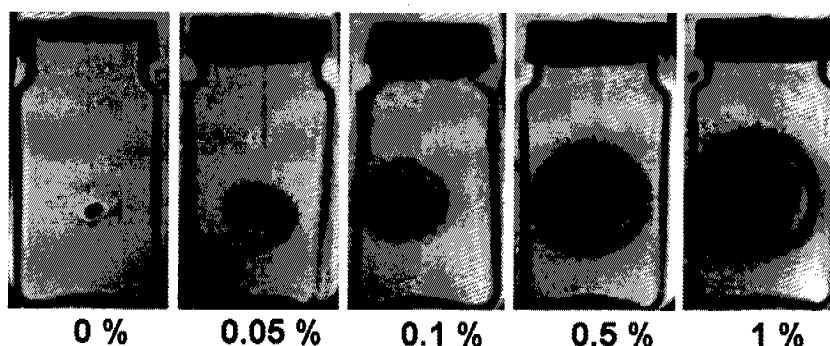
Susceptibility artifacts originated by the  $Fe_3O_4$  marked tablets were quantified as the largest diameter of the circular shaped artifact area. The artifact diameter remained constant over the complete study period for each  $Fe_3O_4$  concentration.

The effect of  $Fe_3O_4$  tablet concentration on the artifact diameter was analyzed (Figure 2.6) and agreed well with theory.<sup>105</sup> The  $Fe_3O_4$  concentration of 1% per tablet volume (4 mg) was chosen to be further evaluated *in vivo*.

#### *Gd-DOTA as drug model*

Recent studies conducted in our group demonstrated that *Gd*-DOTA as a drug model inside a gelatine capsule allow the analysis of distribution and mixing of the drug model in the food-filled human stomach (10, 11). Due to the higher molecular weight compared

a.



b.

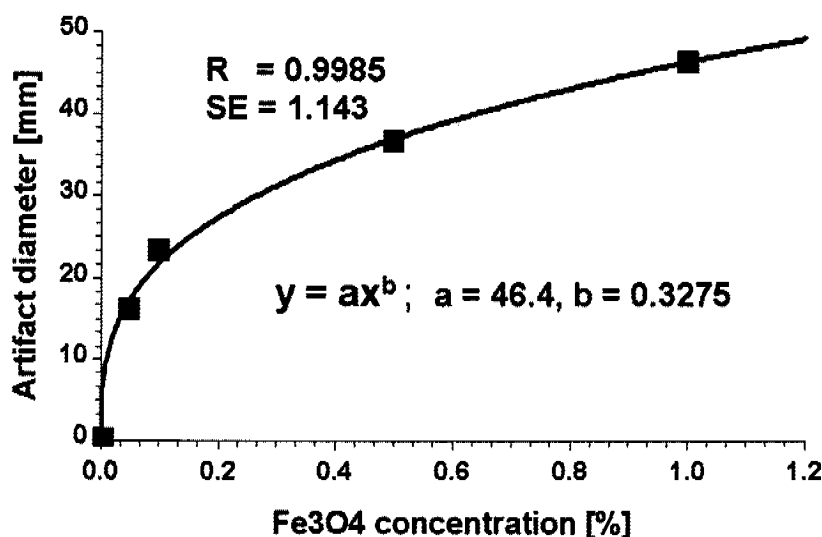


Figure 2.6: (a) Sagittal  $T_1$ -weighted fast spoiled gradient echo MRI images showing susceptibility artifacts of differently marked tablets in water of pH 4.5 and 37 °C (8/150 ms, flip angle of 60 °). Concentrations are given as %  $Fe_3O_4$  in tablet volume. (b) The graph describes the dependency of the originated susceptibility artifact diameter in the MRI images on the  $Fe_3O_4$  concentration in the tablet. There was a strong increase in artifact diameter between concentrations of 0.05% (0.2 mg) and 0.1% (0.4 mg). At concentrations of 0.5% (2 mg) and 1% (4 mg) the increase in artifact diameter flattened. The filled squares (■) indicate the measured artifact diameters. The solid curve represents the calculated power fit ( $y = ax^b$ ). Function parameters  $a$  and  $b$ , correlation coefficient ( $R$ ) and standard error ( $SE$ ) of the power fit are listed.

to water, *Gd*-DOTA might not represent an ideal drug model. But since convection and shear are the dominant mixing forces in the food filled stomach diffusion and gravity are assumed to have negligible effects on the intragastric distribution of the drug model. To apply *Gd*-DOTA as drug model inside a tablet, it is necessary to prepare a pulverized form of the aqueous *Gd*-DOTA contrast agent. Therefore, DOTAREM<sup>®</sup> (Laboratoire Guerbet, Aulnay-Sous-Bois, France) with concentration of 0.5 mmol/ml was wet granulated with metolose powder, sieved and dried overnight at 50°C to derive the pulverized form of DOTAREM<sup>®</sup> ("dried *Gd*-DOTA"). DOTAREM<sup>®</sup> is a commercially available and clinically widely used extracellular paramagnetic contrast agent for intravenous application in MRI angiography. Its intragastric stability and low toxicity as gastrointestinal contrast agent has been shown previously (7).

Before administration of the *Gd*-DOTA loaded tablets, the dried *Gd*-DOTA had to be tested for intragastric stability. The test revealed that after 36 hours of incubation in artificial gastric juice at 37°C, no difference of free *Gd*<sup>3+</sup> was present for the two preparations.

### *In vivo* study

The study was approved by the Institutional Review Board and informed consent was obtained by all volunteers who participated in the study.

#### *Tablet Preparation*

Three floating tablets (tablets *A*, *B*, *C*) of different density were marked with 1% of  $Fe_3O_4$  per volume unit. This concentration permitted a clear distinction between the tablet and other signal voids such as intragastric air or residual solids of the ingested meal. Tablets *A* and *B* had different tablet compositions but were formed with equal compression force by an hydraulic press. Tablet *C* had the same tablet composition as tablet *B*, but was formed with a higher compression force. A fourth slow-release floating tablet (tablet *D*) containing the dried *Gd*-DOTA was prepared. The dried *Gd*-DOTA was embedded at a concentration of 31% of total tablet volume (155 mg) in the tablet. This tablet (tablet *D*) was also formed using the hydraulic press. Detailed information on tablet composition and formation is listed in Table 2.3.

#### *Study Design*

The four tablets (*A*, *B*, *C*, *D*) were evaluated *in vivo*. Each tablet formulation was administered to five healthy male volunteers (age: 19–38 years; BMI: 19.4–26.3 kg/m<sup>2</sup>). All volunteers had no history of gastrointestinal symptoms or abdominal surgery, and all volunteers fasted at least 6 hours prior to the administration of the tablets. Tablets were ingested after intake of a standardized semi-solid test meal consisting of hamburger (130 g), french fries (160 g), string beans (120 g), fruit salad (200 ml), orange juice (100 ml) and water (300 ml). The total energy content of the meal was 922 kcal. After tablet ingestion, all subjects underwent MRI using a 0.5 T open-configuration MRI system (Signa SP, General Electric Medical Systems, Milwaukee, WI, USA). Subjects were positioned in sitting position and sagittal volume scans covering the total gastric region were performed immediately after tablet ingestion and at 30 min intervals thereafter for a period of 4 hours. Sequence parameters of the scans were:  $T_1$ -weighted FSPGR technique; 24 sagittal slices; field of view, 280 mm; flip angle, 60°; matrix, 256 × 160; slice thickness,

Composition (%)	A	B	C	D
Magnetite ( $Fe_3O_4$ )	1	1	1	-
Citronensremonohydrat	2.5	2.5	2.5	2.5
$NaHCO_3$	2.5	2.5	2.5	2.5
PVP K30	1	1	1	1
Metolose 90SH-4000SR	82	46	46	62
<i>Mg</i> -Stearate	1	1	1	1
Lactose	10	26	26	-
Avicel PH 102	-	20	20	-
Dried <i>Gd</i> -DOTA	-	-	-	31
<b>Formation</b>				
Compression force				
[KN/5s]	3	3	6	3
Tool size [mm×mm]	15×6.9	15×6.9	15×6.9	15×6.9
Tablet weight [mg]	400	400	400	400

Table 2.3: Composition of tablet formulations

8 mm; interslice gap, 0 mm; repetition time ms/echo time ms of 150/8 for tablets *A* – *C* and 68/8 for tablet *D*.

## Data Analysis

### Image Analysis

The intragastric position of tablets *A*, *B* and *C* was determined based on the induced susceptibility artifacts in the sagittal MRI images. Gastric residence time ( $T_{max}$ ) of the tablets was defined as the time between first and last detection of the tablet in the stomach. To analyze gastric emptying of the meal, gastric content was outlined in every image of a volume scan. The area of the outlined gastric content was calculated and multiplied with the slice thickness to obtain the volume of the gastric content as function of time. To determine tablet floating performance, the location of the tablet within the stomach was analyzed at each time point based on the volume scan. Intragastric tablet location was calculated relative to the meal surface in the proximal stomach. Floating performance was defined as the ability of the tablet to swim on the meal surface, expressed as a percentage. A floating performance of 100% corresponded to the tablet located on the meal surface, whereas 0% corresponded to a tablet position at the bottom of the stomach (Figure 2.7a). Absolute (ml) and relative (%) distribution volumes of the released *Gd*-DOTA from tablet *D* were analyzed in the total, proximal and distal stomach. Proximal volume was defined as the volume that was outlined between the most left lateral point of the stomach and the incisura of the lesser curvature (Figure 2.7a). Distal volume was defined as the volume between incisura and pylorus. An intensity threshold was manually selected for each segmented volume of each subject. The total volume inside the outlined gastric region with an intensity above the chosen threshold corresponded to the absolute *Gd*-DOTA distribution volume in ml (Figure 2.7b). The relative *Gd*-DOTA distribution volume (%) was defined as the absolute distribution volume divided by the meal volume of the

respective gastric region. Analysis was performed using a home-built software package implemented in IDL 5.4 (Research Systems Inc., Boulder, CO, USA).

### Three dimensional (3D) Visualization

The stomach, the tablet-induced artifact and the *Gd*-DOTA distribution volume (only for tablet *D*) were visualized in three dimensions (3D) for descriptive analysis of intragastric tablet floating performance and drug model distribution. The visualization was performed by a surface rendering, using IsoSurf v1.5d (<http://svr-www.eng.cam.ac.uk/~gmt11>, Dr. Graham Treece) for mesh generation and 3Space Assistant from TGS Europe (Merignac Cedex, France) for viewing.

### Statistics

Half time of gastric meal emptying ( $T_{50\%}$ ), gastric residence time ( $T_{max}$ ) and floating performance of tablets *A*, *B* and *C* were statistically compared using Analysis of Variance (ANOVA) with repeated measures. The Tukey HSD (honest significant difference) post-hoc test was used for inter-group comparison. For tablet *D*, absolute and relative *Gd*-DOTA distribution volumes were statistically analyzed also using ANOVA. Data were expressed in median (interquartile ranges). A  $P$ -value of 0.05 was considered statistically significant.

## Results

Susceptibility artifacts originated from the 1%  $Fe_3O_4$  marked tablets *A*, *B* and *C* allowed detection of intragastric tablet position in all subjects and at all time points. Figure 3 illustrates the 3D visualization of the stomach volume and tablet position at different time points after oral ingestion. Intragastric floating position of the tablet as well as the reduction in proximal stomach volume during the emptying process could clearly be recognized using the 3D images in all volunteers.

Gastric meal emptying curves are plotted in Figure 2.9. There was no difference ( $P = 0.5$ ) in  $T_{50\%}$  among the volunteer groups that ingested tablets *A*, *B* and *C*: *A*, 89 min (87–99 min); *B*, 114 min (109–125 min); *C*, 121 min (106–147 min). No difference ( $P = 0.6$ ) in  $T_{max}$  was detected between the three tablets: *A*, 240 min (240–240 min); *B*, 240 min (210–240 min); *C*, 150 min (150–210 min). Tablet floating performance over time for each of the three tablets is plotted in Figure 2.10a-c. An overall difference ( $P < 0.05$ ) in floating performance was detected between the tablets: *A*, 93% (95–90%); *B*, 80% (80–68%); *C*, 38% (63–32%). The post-hoc test showed a significant difference ( $P < 0.05$ ) only between tablets *A* and *C*.

Intragastric distribution of the *Gd*-DOTA released from tablet *D* and the intragastric position of tablet *D* could be detected and analyzed in all five subjects (Figure 2.11a). The dynamics of total intragastric *Gd*-DOTA distribution could be clearly visualized using the 3D technique (see Figure 2.11b). The *Gd*-DOTA dispersed along the posterior gastric wall into the distal stomach bypassing most of the meal in the fundus. In the distal part of the stomach, the dissolved *Gd*-DOTA was better mixed with gastric content. The relative and absolute *Gd*-DOTA distribution volumes are plotted over time for total, proximal and distal stomach volume in Figures 2.12a and 2.12b. Relative as well as absolute *Gd*-DOTA distribution volumes showed a difference between the two stomach compartments.

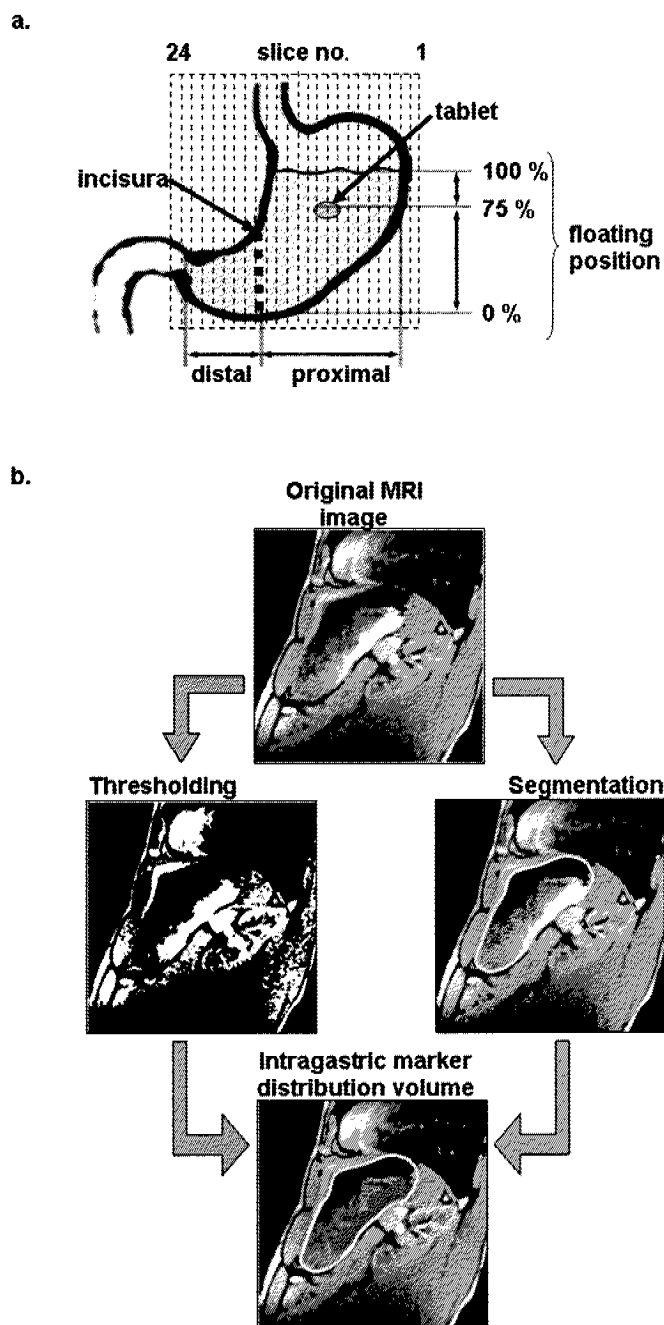


Figure 2.7: (a) Sketch of coronal view of the stomach illustrating the calculation of tablet floating performance based on intragastric tablet position. Sagittal MRI image planes (slice no. 1–24) are depicted as thin dashed lines. The gastric incisura dividing proximal and distal stomach is indicated as bold dotted line. (b) Flow chart that illustrates the technique for calculation of the intragastric distribution volume of the released Gd-DOTA. After segmentation of the stomach volume and applying an image intensity threshold the intragastric marker distribution volume was calculated.



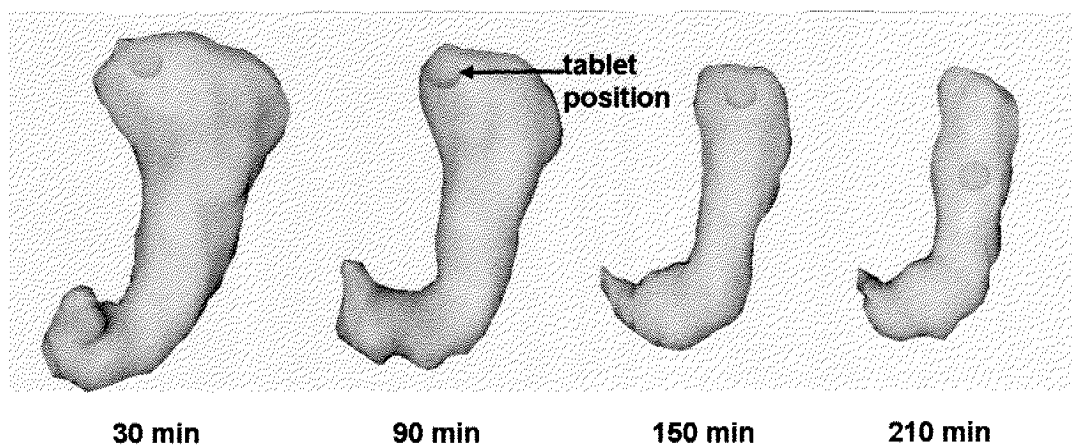


Figure 2.8: 3D visualization of stomach volume and tablet position at times  $t = 30, 90, 150$  and  $210$  min of a volunteer that ingested tablet A. In this volunteer, the tablet was constantly swimming on the meal surface (floating performance of 97%).

Relative distribution volumes ( $P = 0.04$ ) were 9 % (6–12%) in the proximal and 16% (9–33 %) in the distal stomach. Absolute distribution volumes ( $P = 0.01$ ) were 45 ml (27–54 ml) in the proximal and 20 ml (12–29 ml) in the distal stomach. Maximum relative *Gd*-DOTA distribution volumes were 20% in the proximal and 36% in the distal stomach. Maximum absolute *Gd*-DOTA distribution volumes were 54 ml in the proximal and 31 ml in the distal stomach. The maximum distribution of *Gd*-DOTA into the meal was reached after 90 min (90–180 min).

The  $T_{50\%}$  for volunteers that tested tablet *D* was 116 min (79–123 min). The  $T_{max}$  of tablet *D* was 240 min (240–240 min). The floating performance over study period was 94% (87–97%). However, floating power of tablet *D* decreased after 180 min in three subjects.

## Discussion

This study showed that the labeling of gastric-retentive tablets with  $Fe_3O_4$  is feasible and that marked tablets can be visualized using MRI. By using an open-configuration MRI system, intragastric position of tablets could be monitored in seated volunteers. This permitted analysis and quantification of tablet residence time and floating performance in the human stomach under physiological conditions. Furthermore, the study demonstrated that the intragastric release of *Gd*-DOTA as drug model within a gastric-retentive tablet can reliably be monitored using MRI, allowing the analysis of intragastric *Gd*-DOTA distribution volumes.

To the best of our knowledge, this was the first investigation demonstrating the feasibility of MRI to study the impact of formulation density and meal emptying on the dynamics and behavior of ingested gastric retentive tablets in the human stomach. The investigation in the seated position using an open-configuration MRI system has the advantage to represent the most physiological position for eating. As opposed to the supine position, in sitting position the intragastric air and thus the intragastric meal surface is always

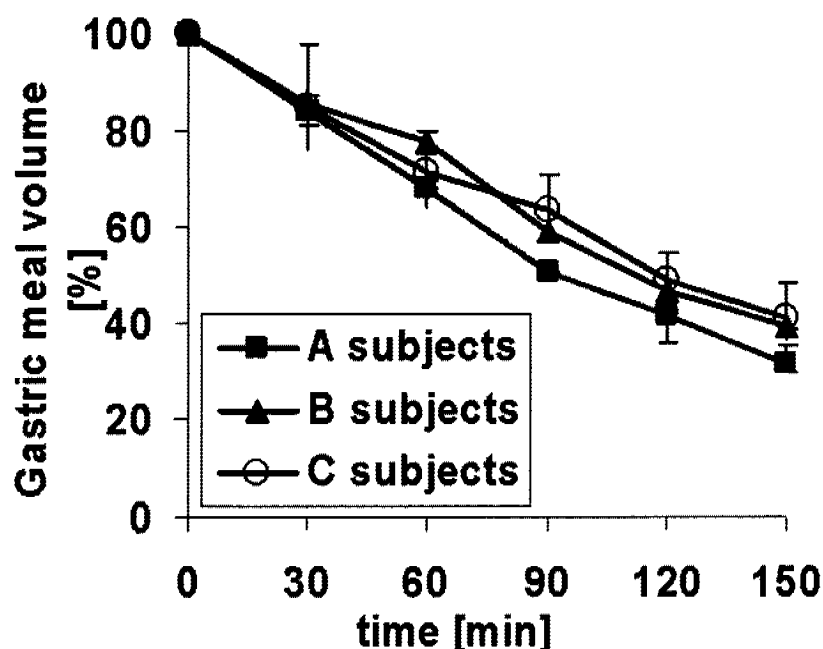


Figure 2.9: Gastric meal emptying curves of the three groups of volunteers that tested tablets A, B and C. Data are plotted as median (interquartile range).

located in the proximal stomach. Gravity acting on a tablet floating on the meal surface is therefore confined along the long gastric axis.

So far,  $\gamma$ -scintigraphy is the most widely used imaging modality for *in vivo* investigation of the delivery and biodistribution of orally ingested drug delivery systems.<sup>32,34</sup> The strength of the scintigraphic method is the ability to quantify the marker distribution (as distribution of activity) based on the count rates in a region of interest that represent a proportion of the radioactivity administered. However, for an accurate quantification it is necessary to determine correction factors for the attenuation of the  $\gamma$ -rays and for the background noise. This demands for simultaneous recordings in anterior and posterior views as well as experimental studies using phantoms.<sup>30</sup> In comparison, the quantification of the drug model distribution using MRI requires the assessment of a calibration curve to determine the signal enhancement of different marker concentrations in the test meal. Also, homogeneous excitation and signal detection over the region of interest is favorable to avoid complex intensity correction procedures. This method has the disadvantage of not allowing simultaneous correction of signal intensity shifts due to fat and/or gastric secretion.

The major drawbacks of scintigraphy are the lack of soft-tissue contrast, the limited spatial resolution and the exposure to ionizing radiation. These limitations may be overcome with MRI. As shown in this study, a 3D gastric volume data set with high spatial and temporal resolution resulting in a good image quality could be obtained in all volunteers. The technique allows for repeated imaging over the time period needed. Future studies will evaluate if the technique is also useful for simultaneous assessment of complementary physiological data including gastric motility and/or gastric accommodation in sitting

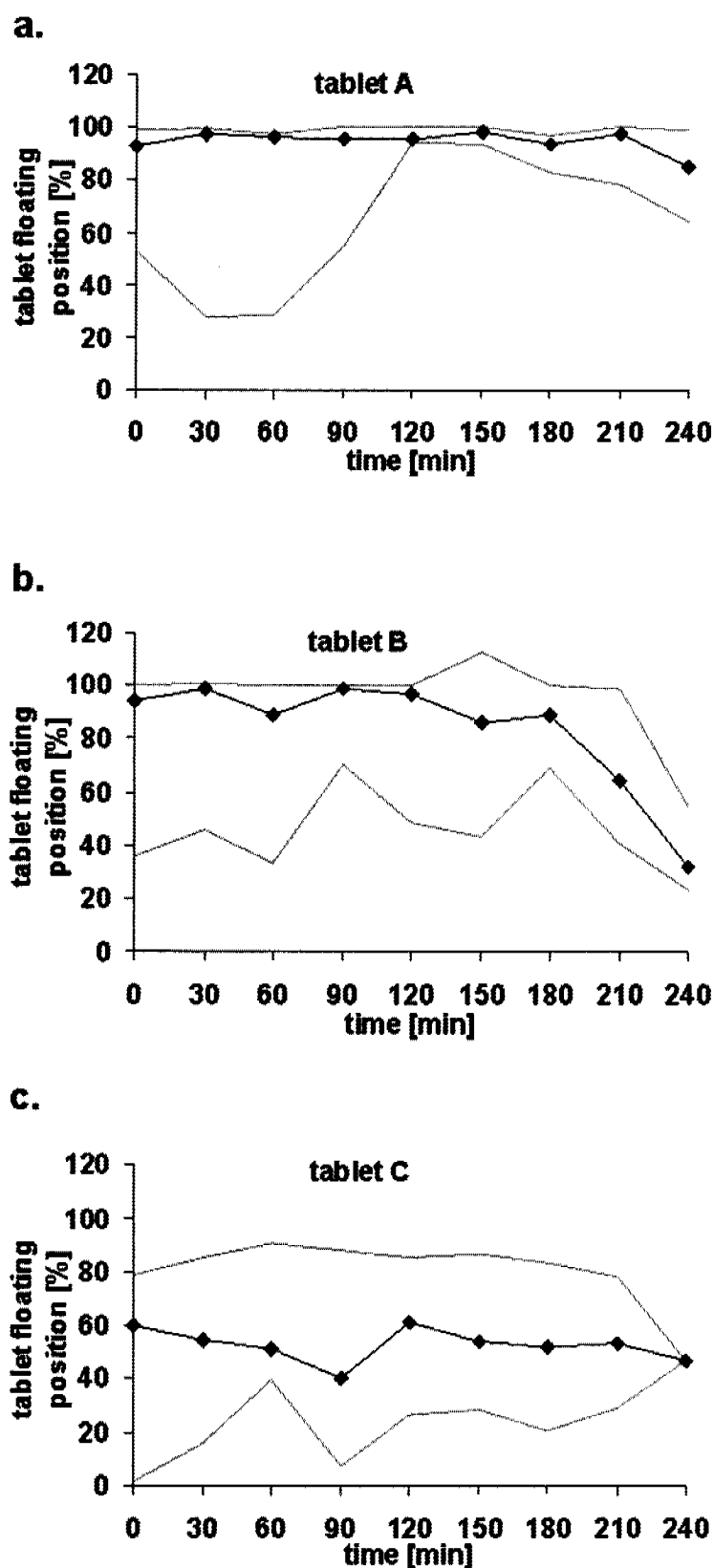


Figure 2.10: (a-c) Tablet floating performance over study period in % for the three tablet formulations A, B and C as measured in the volunteers. Data are plotted as median (min to max range).

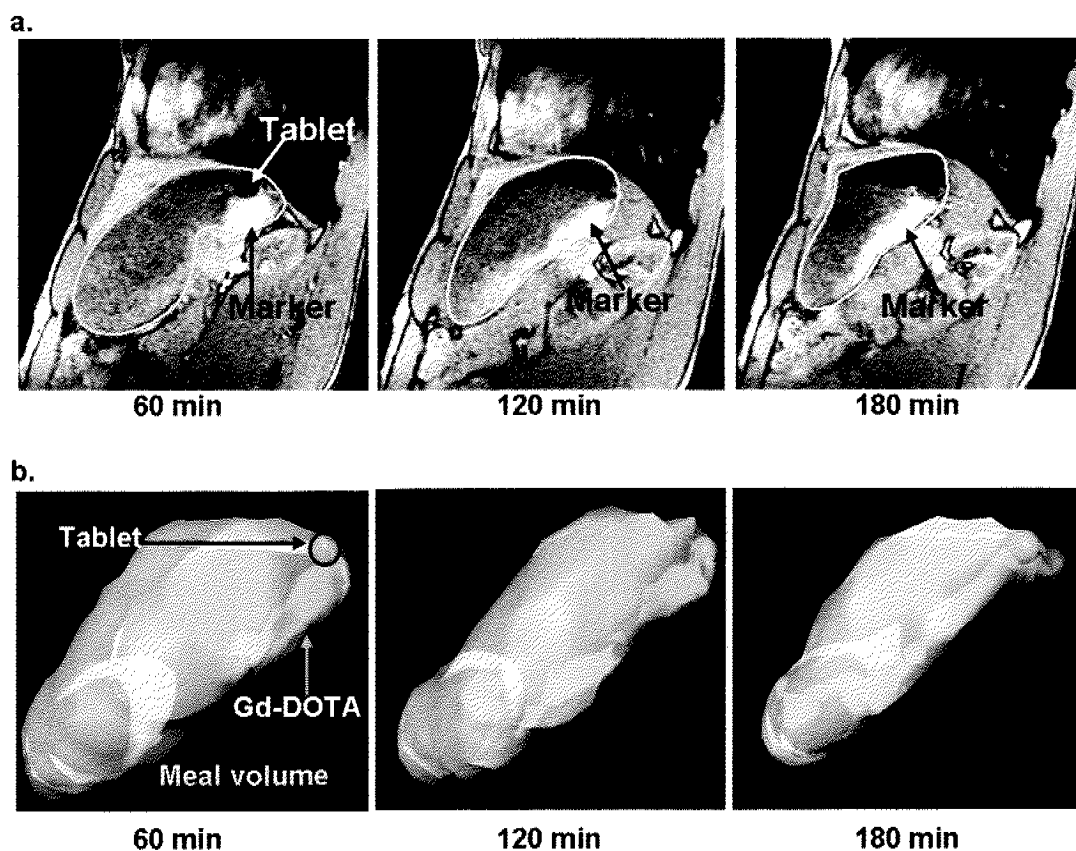
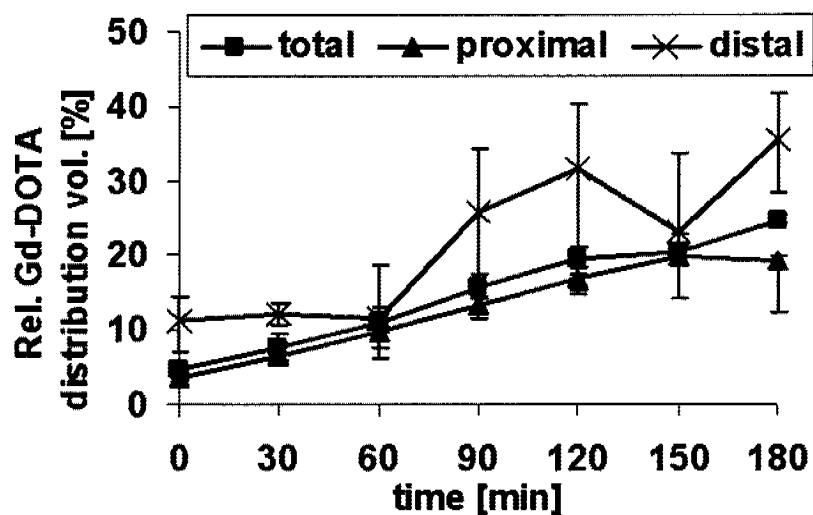


Figure 2.11: **(a)** Sagittal  $T_1$ -weighted fast spoiled gradient echo MRI images (8/68 ms, flip angle of  $60^\circ$ ) of the proximal stomach at times  $t = 60, 120$  and  $180$  min showing the release and intragastric distribution of Gd-DOTA in a volunteer. Stomach volume is outlined and the Gd-DOTA distribution volume as bright signal inside the segmented area is indicated in the MRI images (black arrows). **(b)** 3D visualization of the measured volume scans from **a.** depicting the dynamic of intragastric Gd-DOTA distribution volume in the meal volume.

a.



b.

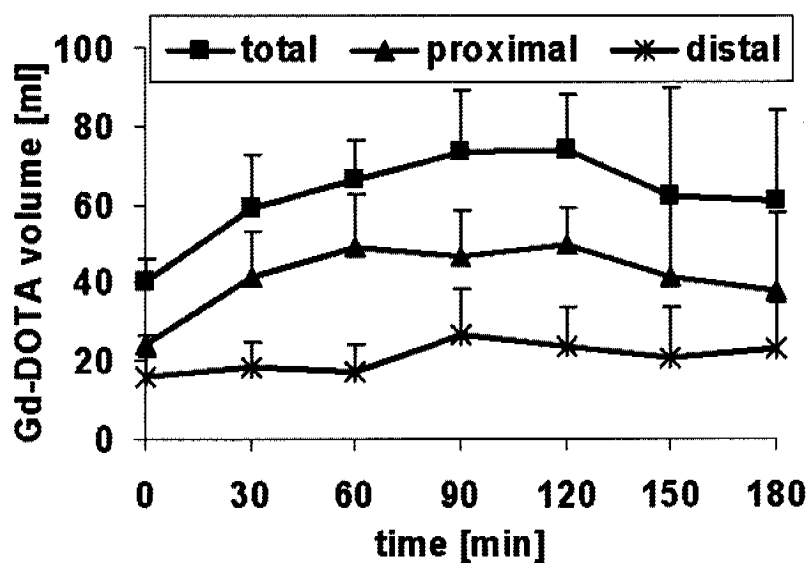


Figure 2.12: (a) The graph shows the relative Gd-DOTA distribution volumes in the total, proximal and distal stomach for tablet D as measured in the human volunteers. (b) The graph shows the absolute Gd-DOTA distribution volumes in the total, proximal and distal stomach for tablet D as measured in the human volunteers. Data are plotted as median (interquartile range).

position. Recent studies have demonstrated the feasibility of MRI for the assessment of gastric function using a closed configuration magnet with the patient lying in supine position.<sup>17,51</sup>

For labeling the gastric-retentive tablet, we used superparamagnetic iron oxide ( $Fe_3O_4$ ) particles and gadolinium chelates ( $Gd$ -DOTA) which are both widely used for abdominal MRI.<sup>38,106–110</sup> The applied  $Fe_3O_4$  (Magnetite) is used as additive (E 172) in food processing with an allowed daily intake of 0.5 mg/kg. This low toxicity combined with low costs makes  $Fe_3O_4$  the preferred MRI contrast marker for tablet labeling. The application of  $Gd$ -DOTA as non toxic and stable gastrointestinal MRI contrast agent has been shown previously.<sup>50</sup>

The optimal  $Fe_3O_4$  concentration of 1% per tablet volume to label the floating tablet was determined in an initial *in vitro* study. Susceptibility artifacts, revealing the intragastric position of ingested  $Fe_3O_4$  marked tablets could be detected in all subjects and over entire study period. Good contrast between gastric content and intragastric air in the MRI images resulted in a sharp delineation of intragastric meal level allowing a reliable calculation of tablet floating performance. Tablet floating performance differed only between tablets *A* and *C*, but with no difference in tablet residence time. The higher variability in the floating performance data of tablet *C* can be explained by the increased effect of gastric motility on tablet position. Tablets showing a floating performance of 60% or less were located within and below the gastric region of contraction wave activation. We conclude that the lower density of tablets *A* and *B* achieved with a compression force of 3 kN provide better intragastric floating performance than the density of tablet *C* (compression force 6 kN). The results indicate that floating performance of the tablets can be controlled effectively by adjusting the tablet composition and density.

The study has further demonstrated that the positive contrast agent  $Gd$ -DOTA embedded in a slow-release floating tablet may serve as an ionic water soluble model drug for the analysis of intragastric distribution of orally administered drugs. Furthermore, the released  $Gd$ -DOTA allowed a semi-quantitative measure of the release characteristics of the tablet. The disadvantage of  $Gd$ -DOTA as tablet marker in comparison to  $Fe_3O_4$  is the greater volume necessary for tablet labeling (31% or 155 mg  $Gd$ -DOTA vs. 1% or 4 mg  $Fe_3O_4$ ).  $Gd$ -DOTA's higher ionic character and osmotic pressure also influence the characteristics of the tablet formulation and thus can strongly alter the tablet properties. Tablet *D* showed long gastric residence times and a good floating performance. However, a large inter-subject variance was observed in gastric meal emptying. Nevertheless, tablet floating performances and gastric residence times appeared to be unaffected by these variations. The emptying pathway of the released  $Gd$ -DOTA proceeded along the inner gastric curvature resulting in an inhomogeneous intragastric distribution. The release of  $Gd$ -DOTA from the tablet was faster than its emptying from the stomach during the first half of the study period (90 min) as shown by the increasing absolute  $Gd$ -DOTA distribution volume in the stomach. The constant increase of relative intragastric drug model distribution volume suggested that more non-marked meal constantly emptied from the stomach while  $Gd$ -DOTA was simultaneously added to gastric content. The possibility that marked meal may have emptied more slowly from the stomach than the non-marked meal was unlikely because the drug model mixes with the liquid phase of the meal that has been shown to empty faster than the solid phase.<sup>15,111</sup> The described results are of interest for orally administered drugs that must empty together with specific macronutrient as is the case for enzyme preparations in chronic exocrine pancreatic insufficiency.<sup>112</sup>

These preparations require homogeneous mixing and simultaneous emptying with the ingested meal to achieve optimal efficacy.

The emptying pathway of the drug model along the inner gastric wall and the non-homogeneous mixing, especially in the proximal part, is in agreement with results of a previous study.<sup>38</sup> In that paper, the higher maximum distal relative distribution volume may be explained by the fact that a liquid marker was used that was instantly released in the gastric fundus. Thus, more *Gd*-DOTA proceeded into the antrum and was mixed in distal meal volume. The similarity of emptying and mixing pattern of the *Gd*-DOTA drug model suggest that these processes might be independent of posture. This observation suggest that the inhomogeneous mixing of liquid and solid phases throughout the stomach may represent an inherent limiting factor for the efficacy of orally administered substances that depend on the interaction with specific macronutrient.

There are some limitations in the proposed approach in this study. A key shortcoming of applying MRI is the limited number of methods for nutrient and drug labeling. Ongoing intensive research on the development of new and more flexible MRI contrast agents may help to overcome these limits in the future which may allow studies comparable to those with dual-isotope imaging.<sup>92</sup> Another shortcoming is the limited availability of the open-configuration MRI scanner used here. However, it should be mentioned that this method can be applied to any compact clinical MRI system. In this case, the effect of posture on intragastric distribution must then be taken into account.<sup>42,44</sup> In conclusion, our study has demonstrated that MRI is useful for assessing the *in vivo* properties of orally ingested gastric-retentive tablets including their floating performance and drug release characteristics. The herein proposed MRI technique may also be useful for studying the gastrointestinal pharmacodynamic and kinetic behavior of newly designed drugs or to evaluate existing drugs. Further studies are needed to evaluate if the technique may replace  $\gamma$ -scintigraphy for these purposes.

## Acknowledgment

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## 2.2.2 Analysis of the meal dependent intragastric performance of a gastric-retentive tablet assessed by magnetic resonance imaging (MRI)

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## Abstract

*Background:* Modern medical imaging modalities can trace labeled oral drug dosage forms in the gastrointestinal tract and thus represent important tools to evaluate the in vivo performance. The application of gastric-retentive drug delivery systems to improve bioavailability and to avoid unwanted plasma peak concentrations of orally administered drugs is of special interest in clinical and pharmaceutical research.

*Aims:* The influence of meal composition and timing of tablet administration on intragastric performance of a gastric-retentive floating tablet was analyzed using magnetic resonance imaging (MRI) in seated position.

*Methods:* A tablet formulation was labeled with iron oxide particles as negative MR contrast marker to allow the monitoring of tablet position in the food-filled human stomach. Labeled tablet was administered together with three different solid meals to volunteers seated in an 0.5 T open configuration MRI system. Volunteers were followed over a four-hour period.

*Results:* Labeled tablet was detectable in all subjects throughout entire study. Tablet showed persistent good intragastric floating performance independent of meal composition. Unfavorable timing of tablet administration did have a minor effect on intragastric tablet residence time and floating performance.

*Conclusions:* MRI can reliably monitor and analyze the in vivo performance of labeled gastric-retentive tablets in the human stomach.

**Key words:** stomach; magnetic resonance imaging; drug delivery; tablet performance; superparamagnetic contrast marker

## Introduction

Bioavailability and effectiveness of orally administered drugs can be controlled and optimized by integrating the drugs in gastric-retentive drug delivery systems, based on mucoadhesive, floating, high density and swelling principles.<sup>31,113-115</sup> This is especially important for drugs that act locally in the stomach,<sup>116,117</sup> have a short absorption window in the small intestine<sup>118</sup> or must be released at the site of macronutrient digestion as is the case in pancreatic insufficiency and cystic fibrosis.<sup>112</sup> Medical imaging modalities, such as  $\gamma$ -scintigraphy, are reliable tools to trace labeled oral drug dosage forms in the animal and human gastrointestinal tract and therefore represent important methods to evaluate the in vivo performance of such drug delivery systems,<sup>32,34,93,119-19,96,120</sup> However, most of these techniques suffer from poor temporal and three-dimensional spatial resolution. In addition, scintigraphic methods expose patients or volunteers to ionizing radiation that precludes repetitive study designs.

In a recent study, the feasibility of magnetic resonance (MR) imaging to monitor the intragastric course of a labeled and orally administered gastric-retentive tablet has been demonstrated.<sup>70</sup> The use of MR imaging for this purpose has gained in importance due to the feasibility of labeling tablets with superparamagnetic iron oxide ( $Fe_3O_4$ ) particles.  $Fe_3O_4$ , which is paramagnetic, induces a strong local reduction of the  $T_2$  relaxation time, causing signal void (so called susceptibility artifact) in the resulting MRI images.<sup>106,121-124</sup> Consequently, the intragastric position of an ingested labeled tablet can be traced by susceptibility artifact created in the image. Additionally, the use of MRI has risen in significance due to the development of open configuration MRI systems with a gap between the

magnet rings permitting scanning in the seated position. This technique takes into account the effect of gravity which is of importance when evaluating the in vivo performance of oral drug delivery systems. Currently, experimental data are lacking concerning the impact of meal composition and intake time on the intragastric performance of gastric-retentive tablets. Therefore, in this study, we used an open configuration MRI system to evaluate the in vivo performance of a  $Fe_3O_4$  labeled gastric-retentive tablet in relation to different meals in the stomach of asymptomatic volunteers, with special emphasis on intragastric tablet position and residence time.

## Materials and Methods

The study was approved by the Institutional Review Board and informed consent was obtained by all volunteers who participated in the study.

### Study population

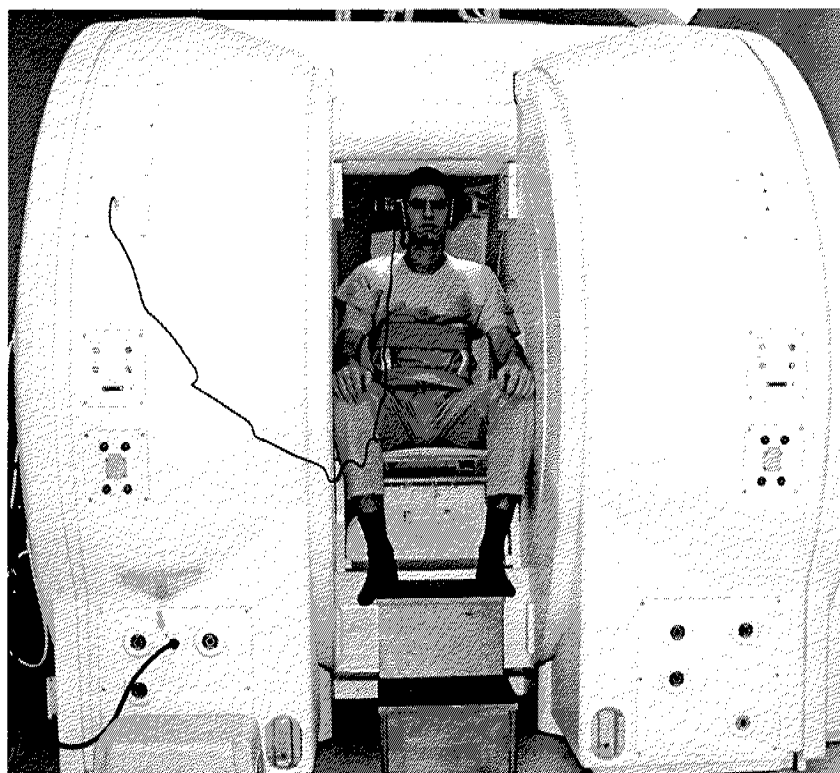
A total of 20 healthy male volunteers (age: 19 - 38 years; body mass index: 17.9 - 26.3 kg/m<sup>2</sup>) participated in the study. Volunteers were instructed to arrive fasted on the study day or to have a light and fat-free breakfast at least 6 hours prior to the onset of the measurements. 15 of these volunteers were randomly divided into three “meal groups”, i.e. hamburger meal, cheese meal and pasta meal, to study the influence of test meal composition on intragastric tablet position. The composition of each test meal is listed in table 2.4. Within each meal group, the volunteers consumed the same meal. The remaining five volunteers were assigned to a “challenge group” to study the influence of the timing of tablet administration, referred to as the “challenge test”. These five volunteers consumed the hamburger meal under the same conditions as above, but with the tablet ingested at a different time point (described below).

### Tablet formulation

A floating tablet formulation was labeled with  $Fe_3O_4$  crystallites as “negative” MR contrast marker (i.e. it creates a signal void in the image). Tablets were prepared in house at the pharmacy of the University Hospital. The tablet composition was as follows:  $Fe_3O_4$  crystallites (1 %), Citric-acid-monohydrate (2.5 %),  $NaHCO_3$  (2.5 %), polyvinylpyrrolidone (PVP) K30 (1 %), Metolose 90SH-4000SR (82 %),  $Mg$ -Stearate (1 %), Lactose (10 %).  $Fe_3O_4$  crystallites were thoroughly mixed with tablet compounds before the drying of tablet powder and final tablet formation. Tablets were formed with a hydraulic press using a tool size of 15 mm  $\times$  6.9 mm and a compression force of 3 kN for 5 seconds. Tablet weight was 400 g.

	Meal composition	Weight (g)	Fat (g)	Energy (kcal)
<b>Hamburger meal</b>	Hamburger	130	15.6	250.9
	French Fries	160	20.8	448
	Green beans	120	0	42
	Orange juice	100	0	45
	Water	300	0	0
	Fruit salad	200	0	136
	<b>Total</b>	1010	36.4	921.9
<b>Cheese meal</b>	Camembert	40	13.4	153.2
	Curd cheese	90	14.4	189
	Whipped cream	20	4.44	51.4
	Potatoes	200	0	160
	Orange juice	100	0	45
	Water	300	0	0
	Fruit salad	200	0	136
	<b>Total</b>	950	32.24	734.6
<b>Pasta Meal</b>	Pasta	150	0	211.5
	Minced meat	120	14.4	231.6
	Olive oil	20	20	176.8
	Onions	100	0	38
	Tomatoes	300	0	96
	Orange juice	100	0	45
	Water	300	0	0
	Fruit salad	200	0	136
	<b>Total</b>	1290	34.4	934.9

Table 2.4: Composition of the test meals



*Figure 2.13: Seated volunteer with fixed abdominal surface coil in 0.5 T open configuration MRI system.*

### **Influence of test meal composition**

Volunteers were asked to eat the meal within 15 min. Immediately after completion of the meal, the marked floating tablet was ingested together with 50 ml of water. Subsequently, each volunteer was placed in sitting position in the 0.5 T open configuration MRI system (Signa SP, GE Medical Systems, Milwaukee, WI) as shown in Figure 2.13. A standard send-receive surface coil for abdominal MRI was wrapped around the upper abdomen of the volunteer for signal reception. MR measurements were taken at 30 min intervals for at least 180 min and at most up to 240 min. At each time point, a stack of 24 sagittal MRI images covering the total gastric region (volume scan) were acquired within three breath holds of 25 seconds using a  $T_1$ -weighted fast spoiled gradient echo (FSPGR) sequence (repetition time, 150 ms; echo time, 8 ms; flip angle,  $60^\circ$ ; field of view, 280 mm; slice thickness, 8 mm; interslice gap, 0 mm; matrix,  $256 \times 160$ ). The volunteers were not allowed to drink or eat during the four-hour study period. However, they were allowed to move freely between the measurements.

### **Challenge test (Influence of the timing of administration)**

To assess the effect of the timing of tablet administration, i.e. to investigate tablet floating performance under suboptimal conditions, the five volunteers were asked to ingest the tablet after completion of the first quarter of the total meal. Ingesting the tablet during meal intake instead of after meal ingestion is potentially challenging for the tablet, since

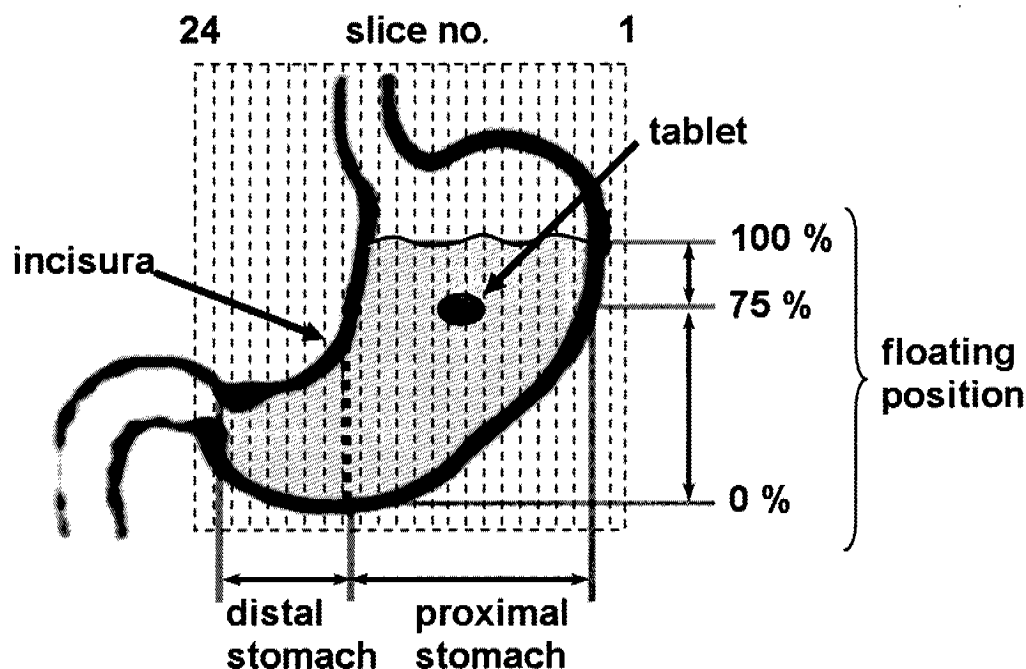


Figure 2.14: Sketch of coronal view of the stomach illustrating the calculation of tablet floating performance from intragastric tablet position. Sagittal image planes (1-24) are depicted as thin dashed lines. Gastric incisura dividing proximal and distal stomach volume is indicated as bold dotted line.

it has to float up passing the incoming meal in order to retain good intragastric floating performance. After meal intake, MR imaging in sitting position was performed in the same way and at same time intervals as described above.

## Data Analysis

### Image Analysis

Gastric residence time of the tablet  $T_{max}$  was determined and defined as the time between first and last detection of the tablet in the stomach. To analyze gastric emptying of the meal, gastric content was outlined in every image of a volume scan acquired during the first 180 min. The area of the outlined gastric content was calculated and multiplied with the slice thickness to obtain the volume of gastric content which was then plotted over time. To determine tablet floating performance, the location of the tablet within the stomach was analyzed at every time point based on the acquired volume scan. Intragastric tablet location was calculated relative to the meal level. Floating performance was expressed in percentage and was defined as the ability of the tablet to stay afloat on the meal surface. A value of 100 % corresponded to a tablet floating at the meal surface and a value of 0 % corresponded to a tablet positioned at the bottom of the stomach (Figure 2.14). Analysis was performed using the medical image processing software eFilm Workstation 1.5.3 (eFilm Medical Inc., Toronto, ON, Canada) and a home-built software package implemented in IDL 5.4 (Research Systems Inc., Boulder, CO 80301, USA).

### Statistical Analysis

The gastric residence time and floating performance of the tablet and the gastric emptying of the different meals (hamburger, cheese, pasta) were compared using Analysis of Variance (ANOVA) with repeated measures. Tablet floating performance observed in the challenge test was compared to the corresponding data of the hamburger group. Data were expressed and plotted as median (interquartile ranges).  $P < 0.05$  was considered statistically significant.

### 3D Visualization

Three-dimensional (3D) visualization of the stomach or meal volume together with the tablet was performed for descriptive analysis of intragastric tablet performance. A surface triangulation based on the outlined contours of the stomach or meal volume and the tablet was applied using a freely available software tool called IsoSurf v1.5d (<http://svr-www.eng.cam.ac.uk/~gmt11>, Dr. Graham Treece). The resulting three-dimensional surface points were then visualized with a 3D CAD/CAM Viewer, 3Space Assistant from TGS Europe (F-33708 Merignac Cedex, France).

## Results

### Influence of meal composition

Tablet administration was well tolerated by all volunteers in the three meal groups (hamburger, cheese and pasta). MR imaging could be performed at all time points for all volunteers. The susceptibility artifact originated from the  $Fe_3O_4$  labeled tablet allowed the detection of the intragastric tablet position throughout the entire study period. The average diameter of the circular artifact area as detected in the sagittal MRI images was 40 mm. Figure 2.15 shows typical sagittal MRI images depicting gastric content and tablet artifact of a volume scan at time  $t = 90$  min for one volunteer of each test meal. Figure 2.16 depicts the 3D visualization of meal volume and tablet in a volunteer (hamburger meal) at times  $t = 60, 120, 180$  min. Gastric emptying curves of the different meals are plotted in Figure 2.17a. Gastric emptying was not statistically different ( $P = 0.71$ ) between the three meal groups. The half times of gastric emptying ( $T_{50\%}$ ) were as follows: hamburger, 89.1 min (85.1 - 99.2 min); cheese, 88.0 min (78.7 - 98.6 min); pasta, 104.8 min (81.3 - 121.7 min). No difference ( $P = 0.77$ ) in tablet residence time  $T_{max}$  was detected between the three test meals: hamburger, 240 min (240 - 240 min); cheese, 240 min (240 - 240 min); pasta, 240 min (240 - 240 min). In one subject of each meal group, the floating tablet emptied before the end of study period (hamburger, 90 min; cheese, 180 min; pasta, 180 min). Tablet floating performances for the three meals are plotted over time in Figure 2.17b. No difference ( $P = 0.72$ ) in tablet floating performance was determined among the meals: hamburger, 94.8 % (80.0 - 97.7 %); cheese, 96.0 % (92.4 - 98.5 %); pasta, 97.7 % (87.9 - 99.2 %).

### Challenge test

The half time of gastric emptying ( $T_{50\%}$ ) for the challenge group was 118.6 min (112.1 - 126.1 min). Gastric residence time of the tablet  $T_{max}$  was 240 min (240 - 240 min).

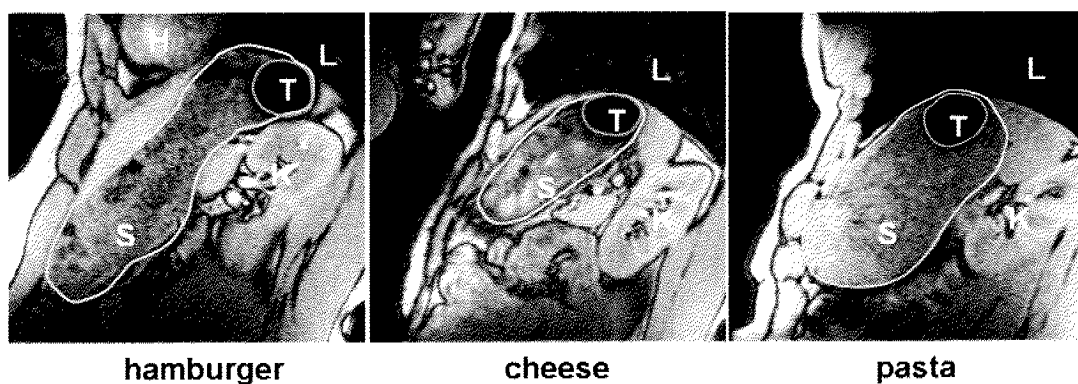


Figure 2.15: Sagittal MRI images showing outlined gastric volume and tablet artifact from each of the meals at time  $t = 90$  min. The size of the artifact is different from the size of the tablet, depending on the  $\text{Fe}_3\text{O}_4$  concentration in the tablet. Stomach wall, tablet artifact and anatomical landmarks are indicated with capital initial letters. T = tablet; S = stomach; H = heart; L = lung; K = kidney.

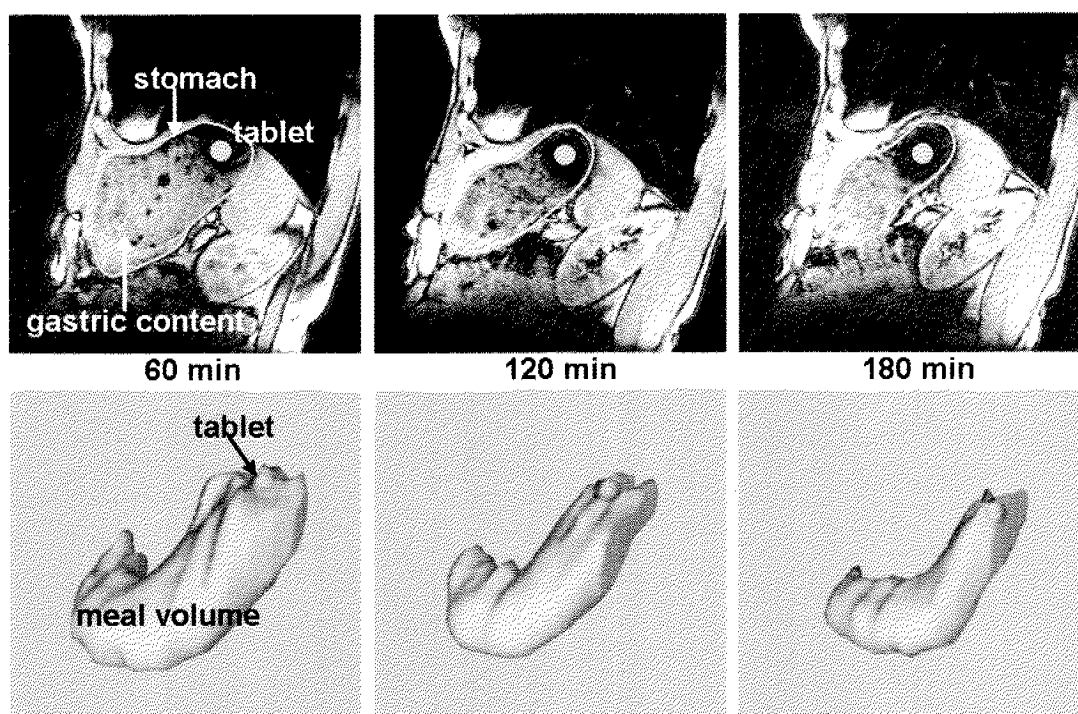


Figure 2.16: Sagittal MRI images of volume scans and corresponding 3D visualization of meal volume and tablet in a volunteer of the hamburger group at times  $t = 60$ , 120 and 180 min. Tablet floating position on the meal surface in proximal gastric volume is nicely depicted.



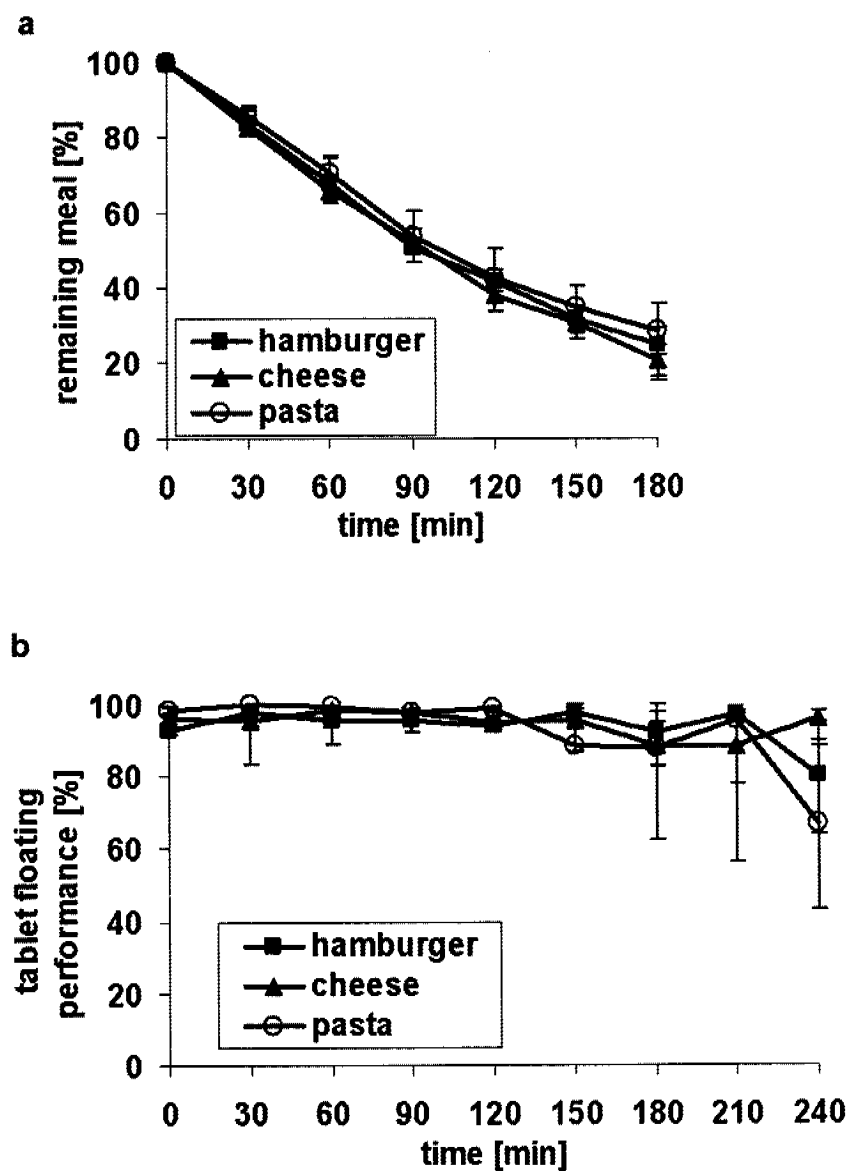


Figure 2.17: (a) Gastric emptying curves of the meal groups over 180 min. (b) Tablet floating performance in % over 240 min for the three meal groups (hamburger, cheese, pasta).

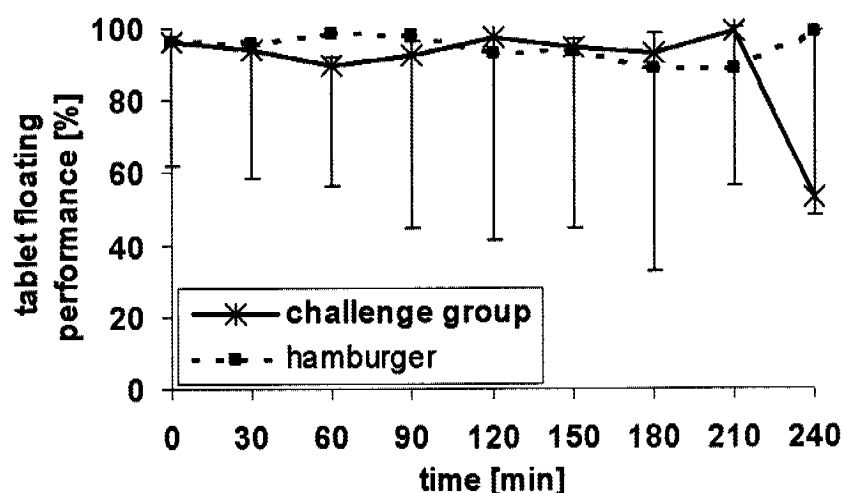


Figure 2.18: Tablet floating performance in % over 240 min for the challenge group (solid line) and the corresponding hamburger group (dotted line).

Also, in one subject from this group, the floating tablet emptied before the end of study period, at time  $t = 120$  min. The floating performance of the tablet in the challenge group is plotted over time in Figure 2.18. The variation of tablet floating performance was greater in the challenge group than in the other analyzed groups. No difference ( $P = 0.36$ ) in tablet floating performance was determined between the challenge group and the hamburger group: challenge, 92.6 % (51.8 - 97.9 %); hamburger, 94.8 % (80.0 - 97.7 %).

## Discussion

The oral delivery of drugs to the human systematic circulation is of major interest because it represents the most convenient and popular way of drug administration for patients and physicians. Gastric-retentive oral drug delivery systems were developed to optimize the time course of intestinal delivery for specific drugs, e.g. drugs that require interaction with specific macronutrient or have a short intestinal absorption window. In combination with timed release, these delivery systems can improve the bioavailability of drugs and lower toxicity due to the reduction of unwanted drug plasma peaks.

In this study, the intragastric floating performance and residence time of a gastric-retentive tablet administered together with different semi-solid meals were determined by MRI in the seated position. In all subjects tablets showed good persistent intragastric floating performance. Tablet floating performance and residence time showed no dependency on meal composition as well as the time of administration. The use of an open-configuration MRI system provided the unique opportunity to evaluate the tablets intragastrically in a seated position.

The experimental set-up permitted volunteers to move freely in between measurements that is essential for a four-hour study period. In comparison to more established imaging techniques such as  $\gamma$ -scintigraphy, X-rays and ultrasound, MRI has the advantage of

imaging the complete three dimensional gastric volume at high spatial and temporal resolutions and adjustable image contrast. Also, MRI does not involve exposure to ionizing radiation and allows the performance of repeated studies in healthy volunteers. Finally, MRI allows the assessment of complementary physiological data of gastric function as shown in recent studies by Kunz et al.<sup>16</sup> and Marciani et al.<sup>125</sup> using whole body MRI systems.

The intragastric floating performance and residence time of the ingested  $Fe_3O_4$  marked tablet were determined by localizing and analyzing the originated susceptibility artifact in the MRI images. The susceptibility artifact was clearly detectable in all MRI images and distinguishable from other intragastric signal voids such as air or solid pieces of meal and thus permitted a reliable calculation of tablet performance. The three-dimensional visualization of the MR data better illustrated the intragastric position of the tablet relative to gastric content and proved helpful for the understanding of the tablet's intragastric pathway.

The results of this study showed that there were no differences in gastric meal emptying, tablet floating performance or tablet residence time between the three test meals. This may not be surprising given the small number of analysed subjects ( $n = 5$ ). However, the plotted data (Figure 5) and the medians and interquartile ranges listed in the 'Results' section do not indicate the emergence of any trend. This suggests that the non-significant results are due to the small differences of these parameters between the meals rather than to the small sample size. As mentioned, no difference in gastric meal emptying was determined. Nevertheless, for each meal group noticeable inter-subject variations were observed. The observed inter-individual and intra-individual variations for gastric emptying are consistent with those reported in the literature.<sup>126</sup> The administered tablet showed persistent good floating performance in all volunteers independent of the meal composition. Nevertheless, for each meal, one subject emptied the tablet before the end of the study period. For this subject in the hamburger meal group, the tablet showed a poor floating ability immediately after intake and was emptied after only  $t = 90$  min. This effect might be explained by the particular gastric anatomy of this particular volunteer. More meal volume was stored in the distal stomach than in the gastric fundus, as opposed to what is typically observed in other volunteers. We assume that in this subject the cardia was positioned very low explaining the low initial intragastric position of the ingested tablet in relation to the meal surface. For the subjects from the cheese meal and pasta meal group with early gastric emptying, the tablet started to lose floating ability after time  $t = 180$  min and was emptied afterwards. Interestingly, both volunteers also had the lowest value for half time of gastric emptying in the respective meal, suggesting an influence of the gastric emptying pattern on intragastric tablet performance. However, the similarity of gastric emptying characteristics for the different meals did not allow to analyze the influence of gastric emptying on tablet floating performance in this study. The described observations highlight the potential problems for the development of an optimal gastric-retentive tablet formulation. To assure a constant and complete intragastric release of the drug in the stomach, the release characteristic must be adjusted according to the intragastric residence time of the tablet. This parameter however may be effected by individual differences in gastric anatomy and gastric emptying. The tablet analyzed in the challenge group (the floating tablet was administered during the meal instead of afterwards) also showed a persistent but more variable floating performance. As in the other groups, the tablet emptied earlier in one subject. This result indicates

that the floating performance of the tablet is not significantly affected by its ingestion during or after the meal. Today, the efficacy of most pharmaceuticals is evaluated by analyzing the pharmacokinetics using repeatedly collected blood or saliva samples from a large number of subjects.<sup>127</sup> In such studies, the influence of the drug delivery system on the bioavailability of the drug remains unspecified. Studies conducted to investigate effects of newly developed sophisticated delivery systems are usually performed *in vitro* or in animals. From the results derived in this study, we conclude that *in vitro* or animal studies alone will not be sufficient to reliably predict intragastric fate and dynamics of oral drug delivery systems and thus also of the administered drugs in the human gastrointestinal tract. More extensive human studies are needed to collect a comprehensive knowledge about the fate of different drug delivery systems and applied drugs in the human body. This would enable the development of highly sophisticated and specified systems that can further improve and control the bioavailability and effectiveness of administered drugs. In the future, MRI as non-invasive and radiation free imaging tool might attain equal importance as  $\gamma$ -scintigraphy in this field of research.

## Acknowledgment

We acknowledge the technical and organizational support of Karl Treiber and Bernadette Stutz. The study was supported by F. Hoffmann-LaRoche, Basel, Switzerland and the Swiss National Science Foundation (SNF grants 32-54056.98 and 31-55932.98).

### 2.2.3 Intragastric performance of a slow-release, single-unit sinking tablet assessed by magnetic resonance imaging (MRI)

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## Abstract

**Purpose:** To use seated MRI for *in vivo* monitoring the post-prandial intragastric performance of single-unit, sinking tablets under physiological conditions in asymptomatic volunteers.

**Methods:** Four sinking tablets ( $S_{1-3}$  and  $G$ ) of different density and size were marked with either 1% of  $Fe_3O_4$  or 20%  $Gd$ -DOTA (drug model) and ingested during meal ingestion. Tablet  $S_1$  was further tested in three different meals (hamburger, cheese, pasta). MR imaging in the seated body position was performed to detect post-prandial tablet sinking performance. Tablet performance was analyzed in terms of intragastric tablet position (relative position to intragastric meal level), movement and residence time ( $T_{max}$ ) as well as intragastric distribution volume of drug model (% of meal volume). **Results:** No difference was found for tablet sinking performance ( $S_1$ , 73% vs.  $S_2$ , 75% vs.  $S_3$ , 72% vs.  $G$  = 65%). Almost exclusively, the large size tablets and  $G$  remained inside the stomach for the complete study period ( $S_1$ , 240 min vs.  $S_2$ , 210 min vs.  $S_3$ , 150 min vs.  $G$ , 240 min). There was a difference in meal emptying time ( $T_{50\%}$ ) for the three meals (hamburger, 107 min vs. cheese, 89 min vs. pasta, 115 min). Tablet sinking performance of tablet  $S_1$  was not different between meals (70% vs. 82% vs. 77%). For the cheese meal, only one tablet remained in the stomach for 240 min, however no correlation was found between  $T_{50\%}$  and  $T_{max}$ . Tablet  $S_1$  performance was independent of time point of administration. **Conclusion:** Gastroretention of sinking tablets is closely related to their overall size. Large and dense tablets ( $19 \times 8.8$  mm<sup>2</sup>, 1.3 g/ml) are likely to remain in the stomach for 4 hours; however exceptions exist due to anatomical and physiological variability. Monolytic dosage forms of this size can not be regarded as safe gastric retentive dosage forms even in the presence of food.

**Key words:** solid oral dosage form, sinking tablet, human stomach, intragastric tablet performance, magnetic resonance imaging

## Introduction

Gastroretentive dosage forms have attracted increasing attention over the last years. These oral drug delivery systems are designed to remain in the stomach for a desired period of time and to release the drug in a controlled profile over several hours.<sup>29, 103, 128–130</sup> The gastroretentive approach offers advantages for several applications, i.e. for drugs which act locally in the stomach (e.g. antibiotics against helicobacter pylori) or substances that have an absorption window within the gastrointestinal tract (e.g. levodopa). Using gastroretentive systems, the effective period and absorption rate can be increased and food dependency decreased. This improves bioavailability and effectiveness of the applied drug. Despite the efforts made in the recent years, our knowledge about the detailed fate of solid oral delivery systems which are designed to be gastroretentive is still limited. However, detailed knowledge on the *in vivo* properties of orally administered tablets and their interaction with food is essential for the successful development of effective gastroretentive dosage forms.

Magnetic resonance imaging (MRI) is feasible for concurrent assessment of gastric tonic and phasic motility as well as gastric secretion.<sup>19, 20, 60</sup> These characteristics together with the flexible soft tissue contrast, high spatial and temporal resolution and lack of ionizing radiation present considerable advantages of MRI over the gold standard  $\gamma$ -scintigraphy.

It was recently shown by us that MRI is a very valuable imaging technique for monitoring intragastric position of orally ingested GR floating tablets in fed state.<sup>33,70</sup> MRI allowed simultaneous assessment of complementary anatomical and physiological data including (three-dimensional) gastric shape and gastric emptying.

After our previous investigations on floating tablets, we focused the present investigation on high density systems, which have also been proposed as gastroretentive dosage forms.<sup>129</sup> However, compared to floating systems, only few data have been published so far. The purpose of this study was therefore to use seated MRI for the in vivo monitoring of the post-prandial intragastric performance of single-unit, slow release, high density (sinking) tablets under physiological conditions in asymptomatic volunteers. Sinking tablets of different density and size were labeled with superparamagnetic iron oxide ( $Fe_3O_4$ ) particles as tablet marker or were loaded with paramagnetic gadolinium (*Gd*) chelates (*Gd*-DOTA) as model drug. Post-prandial intragastric tablet performance, i.e. intragastric tablet position, tablet residence time, drug model release and distribution was detected and compared for the different tablet formulations. Moreover, tablet performance was compared after ingestion of different meals as well as for different time points of administration. Furthermore, tablet movement in the distal stomach lumen was dynamically imaged and visualized as MRI movies.

## Methods

The study was approved by the Institutional Review Board and informed consent was obtained by all volunteers who participated in the study.

The use of superparamagnetic Iron Oxide ( $Fe_3O_4$ ) particles and paramagnetic *Gd*-DOTA (incorporated in a HPMC matrix by wet granulation and drying) as MRI tablet marker has previously been evaluated and published by our group.<sup>70</sup>  $Fe_3O_4$  particles create a strong negative contrast in the MRI image due to MR signal void in their vicinity.<sup>106,131</sup> *Gd*-DOTA causes also a negative contrast if it is in the solid state in the tablet. However, after release, it is in the solubilized state and provides a distinct positive contrast due to shortening of the  $T_1$  relaxation time of adjacent protons.<sup>50,132</sup>

The following study in human volunteers is divided into two phases. During phase 1,  $Fe_3O_4$  marked tablets of different density and sizes were analyzed for intragastric position and residence time in the human food-filled stomach. The best performing tablet formulation was then labeled with a paramagnetic drug model (*Gd*-DOTA) and intragastric drug model release and distribution was investigated in addition to tablet position and residence time (tablet performance). In phase 2, meal dependent in-vivo performance of the best  $Fe_3O_4$  marked tablet as well as the influence of the timing of tablet administration was studied.

## Tablet Preparation

All tablet formulations were prepared in house at the pharmacy of the University Hospital. Three sinking tablets (tablets  $S_{1-3}$ ) of different density and size were marked with 1% w/w of  $Fe_3O_4$ . This concentration permits a clear distinction between the signal void created by the tablet and other signal voids such as intragastric air or residual solids of the ingested meal.<sup>70</sup> A fourth slow-release, sinking tablet (tablet *G*) containing pulverized *Gd*-DOTA was prepared. The tablet compositions are given in table 2.5. Tablets were

		$S_1$	$S_2$	$S_3$	$G$
Mass [mg]		1000	750	500	1000
Size [mm <sup>2</sup> ]		19×8.8	19×8.8	15×6.9	19×8.8
Com- position [%]	Metolose 90SH	20.0	20.0	20.0	40.0
	4000SR				
	Emcompress	71.0	71.0	71.0	32.0
	Avicel PH 102	5.0	5.0	5.0	5.0
	Fe <sub>3</sub> O <sub>4</sub> -black	1.0	1.0	1.0	–
	Dried Gd- DOTA	–	–	–	20.0
	Mg-Stearate	1.0	1.0	1.0	1.0
	Talcum	2.0	2.0	2.0	2.0

Table 2.5: Composition of tablet formulations

formed using a hydraulic press applying a pressure of 10 kN for 5 seconds. All four tablet formulations were designed to sink to the bottom of the gastric lumen and to have a gastric residence time of at least 4 hours in the presence of a meal.

### Study population

A total of 40 healthy male volunteers (age:  $27 \pm 5$  years; body mass index:  $23 \pm 2.6$  kg/m<sup>2</sup>) participated in the study. All volunteers had no history of gastrointestinal symptoms or abdominal surgery. Volunteers were instructed to arrive fasted on the study day or to have a light and fat-free breakfast at least 6 hours prior to the onset of the measurements. 15 of the volunteers were randomly divided into three “tablet groups”, i.e. tablet  $S_1$ ,  $S_2$  and  $S_3$ , to investigate the in-vivo performance of the different tablet formulations. In 5 volunteers, release and distribution of the drug model marked tablet  $G$  was studied. Another 15 volunteers were randomly divided into three “meal groups”, i.e. hamburger meal, cheese meal and pasta meal, to study the influence of test meal composition on intragastric tablet ( $S_1$ ) position. The remaining five volunteers were assigned to a “challenge group” to study the influence of the timing of tablet ( $S_1$ ) administration, referred to as the “challenge test”.

### Study design

For study phase 1, tablets  $S_{1-3}$  and  $G$  were administered (together with 50 ml of water) after the first quarter of total meal intake of a standardized semi-solid test meal consisting of hamburger (130 g), french fries (160 g), string beans (120 g), fruit salad (200 ml), orange juice (100 ml) and water (300 ml). The total energy content of the meal was 922 kcal.

For study phase 2, volunteers consumed the same meal within each meal group. The hamburger meal was the same as for study phase 1. The cheese meal (735 kcal) consisted of camembert (40 g), curd cheese (90 g), whipped cream (20 g), potatoes (200 g), fruit salad (200 ml), orange juice (100 ml) and water (300 ml). The pasta meal (935 kcal) contained pasta (150 g), minced meat (120 g), olive oil (20 g), onions (100 g), tomatoes (300 g), fruit salad (200 ml), orange juice (100 ml) and water (300 ml). Volunteers were asked to eat the meal within 15 min. After completion of the first quarter of total meal



intake, the  $Fe_3O_4$  marked sinking tablet  $S_1$  was ingested together with 50 ml of water. For the challenge test, the sinking tablet  $S_1$  was administered after completion of meal ingestion (hamburger meal). This is potentially challenging for the sinking tablet, since it first has to sink through all gastric contents in order to be retained inside the gastric lumen for the defined time period.

### MRI measurements

After tablet ingestion, all subjects underwent MR imaging using a 0.5 T open-configuration superconducting MRI system (Signa SP, General Electric Medical Systems, Milwaukee, WI). Subjects were positioned in sitting position on a wooden chair placed between the magnet rings of the open configuration MRI system (figure 2.19a). A standard butterfly send-receive surface coil was placed around the upper abdomen for signal reception. MRI scans acquiring stacks of sagittal image planes covering the total gastric region (volume scans) were performed during three breath-hold periods of 25 seconds immediately after tablet ingestion and at 30 min intervals thereafter for a period of four hours. For tablet group  $S_1$  and the challenge group, a dynamic imaging sequence (motility scan) was performed directly after each volume scans for imaging gastric peristaltic activity. Imaging protocol included a  $T_1$ -weighted spoiled FSPGR sequence with the following parameters for the volume scan: 24 sagittal slices, field of view (FOV) = 280 mm, rectangular field of view (RFOV) = 0.75, flip angle =  $60^\circ$ , matrix =  $256 \times 160$ , slice thickness  $\Delta z = 8$  mm, interslice gap = 0 mm, repetition time (TR)/echo time (TE) of 150/8 ms for tablets  $S_{1-3}$  and 68/8 ms for tablet  $G$ . The motility scan parameters were as follows: 40 dynamics (during gentle breathing), oblique coronal image slice,  $T_{scan} = 89$  s (2.23 seconds per image), TR/TE = 17/8 ms, flip angle =  $60^\circ$ ,  $\Delta z = 10$  mm, matrix =  $256 \times 160$ , FOV = 300 mm, RFOV = 0.75.

## Data Analysis

### Image Analysis

Image analysis of the acquired volume scans has been described in detail in the previous work.<sup>70</sup> Here, we only shortly describe analyzed parameters. Gastric meal emptying curves (decrease in normalized meal volume over time) were derived for each volunteer and half time of gastric meal emptying ( $T_{50\%}$ ) was calculated. Gastric residence time ( $T_{max}$ ) of the tablets was defined as the time between first and last detection of the tablet in the stomach. The location of the tablet within the stomach, relative to the meal surface, was analyzed at each time point (figure 2.19b). Tablet sinking performance, i.e. the ability of the tablet to stay at the bottom of the gastric lumen on the meal surface was expressed as a percentage (100% = tablet sitting at the bottom of gastric lumen; 0% = tablet floating on intragastric meal surface). Absolute and relative distribution volumes of the released drug model from tablet  $G$  were analyzed in the total, proximal and distal stomach. The relative  $Gd$ -DOTA distribution volume (%) was defined as the absolute distribution volume divided by the meal volume of the respective gastric volume (total or proximal or distal). Analysis was performed using a home-built software package implemented in IDL 5.4 (Research Systems Inc., Boulder, CO, USA). Image data of each motility scan were combined into movies visualizing peristaltic contractions and

movements of the sinking tablet within the distal stomach. These served for qualitatively assessment only.

### 3D Visualization

3D-visualization of the meal together with the tablet was performed for descriptive analysis of intragastric tablet performance. A surface triangulation based on the outlined contours of the stomach or meal volume and the tablet was applied using the open source software IsoSurf v1.5d (<http://svr-www.eng.cam.ac.uk/~gmt11>, Dr. Graham Trecece).

### Statistics

750% of the meals,  $T_{max}$  and mean sinking performance over time of the tablet formulations were statistically compared using the Kruskal-Wallis Test. For phase 1, sinking performance of tablets  $S_{1-3}$  and  $G$  were compared for one meal (hamburger meal). In phase 2, tablet  $S_1$  was compared for different meals (hamburger, cheese, pasta). For the challenge test, tablet ( $S_1$ ) sinking performance was compared to the corresponding data of phase 1. For tablet  $G$ , absolute and relative Gd-DOTA distribution volumes were statistically analyzed using a two-way repeated measures ANOVA. All data were expressed and plotted in median (interquartile ranges). A  $P$  value of 0.05 was considered statistically significant.

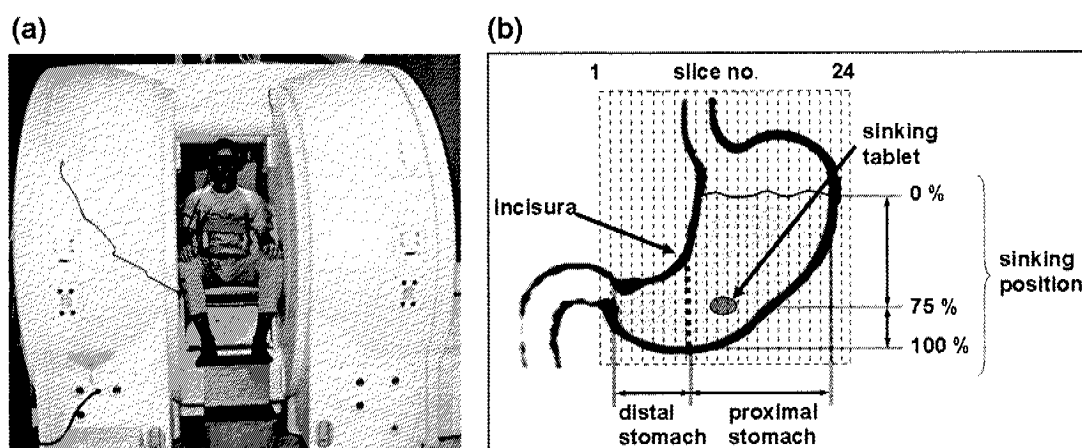


Figure 2.19: (a) Volunteer seated on a wooden chair between the magnet rings of the 0.5 T open-configuration MRI system with fixed standard abdominal send-receive surface coil for MR signal reception. (b) Sketch of coronal view of the stomach illustrating the calculation of tablet sinking performance based on intragastric tablet position. Sagittal MRI image planes (slice no. 1–24) are depicted as thin dashed lines. The gastric incisura dividing proximal and distal stomach is indicated as bold dotted line.

## Results

Tablet administration was well tolerated. Intra-gastric tablet position and meal emptying was successfully monitored in all volunteers. Figure 2.20a shows the intra-gastric position of tablet  $S_1$  over total study period in a representing volunteer of the hamburger group as seen in the MRI images. Corresponding 3D visualizations of meal volume and tablet at times  $t = 30, 90$  and  $210$  min are presented in Figure 2.20b.

Intra-gastric drug model distribution was assessed in all five volunteers that ingested tablet  $G$ . Tablet position and drug model release during the first 90 min as seen in the MRI images of a representing volunteer are depicted in Figure 2.21.

### In-vivo performance of tablets $S_{1-3}$ and $G$

No difference was detected for  $T_{50\%}$  of the hamburger meal among the tablet groups. The number of tablets which remained inside the stomach for total period of 240 min was 4 of 5 for the  $S_1$  group, 1 of 5 for the  $S_2$  group, 0 of 5 for the  $S_3$  group and 3 of 5 for the  $G$  group. No statistical difference between the tablet groups was observed for  $T_{max}$ :  $S_1$ , 240 min (240–240 min);  $S_2$ , 210 min (210–210 min);  $S_3$ , 150 min (120–150 min) and  $G$ , 240 min (210–240 min); n.s. Tablet sinking performance over study period is shown in Figure 2.22a. No difference was found for the tablet formulations:  $S_1$ , 73% (68–81%);  $S_2$ , 75% (69–82%);  $S_3$ , 72% (58–79%);  $G$ , 65% (51–73%); n.s. It was noticeable that the  $Gd$ -DOTA tablet formulation  $G$  showed reduced sinking capabilities, especially at the beginning and towards the end of study period. This is not surprising because the density of the tablet was lower compared to the  $S$  tablet series due to the lower amount of Emcompress (table 1). Although statistics revealed no difference in  $T_{max}$  and sinking performance between tablets, the data clearly indicated tablet  $S_1$  as the best performing sinking tablet. Therefore, tablet  $S_1$  was selected to be further tested in phase 2 of the study.

Although differences in  $T_{max}$  and sinking performance reached no statistical significance between tablets, tablet  $S_1$  was selected to be further tested in phase 2 of the study. Tablet  $S_1$  showed constant sinking performance and longest intra-gastric residence time.

Intra-gastric distribution of the released  $Gd$ -DOTA from tablet  $G$  was detected and analyzed in all five subjects. The absolute and relative  $Gd$ -DOTA distribution volumes are plotted over time for total, proximal and distal stomach volume in Figures 2.22b. Absolute  $Gd$ -DOTA distribution volumes were not different between the two stomach compartments. Absolute distribution volumes were 10 ml (9–23 ml) in the proximal and 15 ml (10–29 ml) in the distal stomach. Relative distribution volumes showed a trend for a difference between proximal (5% (3–6%)) and distal (17% (11–24%)) stomach ( $P = 0.9$ ).

### Meal dependent sinking performance and challenge test of tablet $S_1$

There was a difference in  $T_{50\%}$  between the three different meals: hamburger, 107 min (104–112 min); cheese, 89 min (86–100 min); pasta, 115 min (110–132 min);  $P < 0.05$ . The cheese meal emptied faster compared to the pasta meal but not the hamburger meal. The number of tablets which remained inside the stomach for total period of 240 min was 4 of 5 for the hamburger group, 1 of 5 for the cheese group and 3 of 5 for the pasta group. No statistical difference was detected for  $T_{max}$ : hamburger, 240 min (240–240 min); cheese, 150 min (150–210 min); pasta, 240 min (210–240 min); n.s. No correlation

in table 2.4. Within each meal group, the volunteers consumed the same meal. The remaining five volunteers were assigned to a "challenge group" to study the influence of the timing of tablet administration, referred to as the "challenge test". These five volunteers consumed the hamburger meal under the same conditions as above, but with the tablet ingested at a different time point (described below).

### Tablet formulation

A floating tablet formulation was labeled with  $Fe_3O_4$  crystallites as "negative" MR contrast marker (i.e. it creates a signal void in the image). Tablets were prepared in house at the pharmacy of the University Hospital. The tablet composition was as follows:  $Fe_3O_4$  crystallites (1 %), Citric-acid-monohydrate (2.5 %),  $NaHCO_3$  (2.5 %), polyvinylpyrrolidone (PVP) K30 (1 %), Metolose 90SH-4000SR (82 %), *Mg*-Stearate (1 %), Lactose (10 %).  $Fe_3O_4$  crystallites were thoroughly mixed with tablet compounds before the drying of tablet powder and final tablet formation. Tablets were formed with a hydraulic press using a tool size of 15 mm  $\times$  6.9 mm and a compression force of 3 kN for 5 seconds. Tablet weight was 400 g.

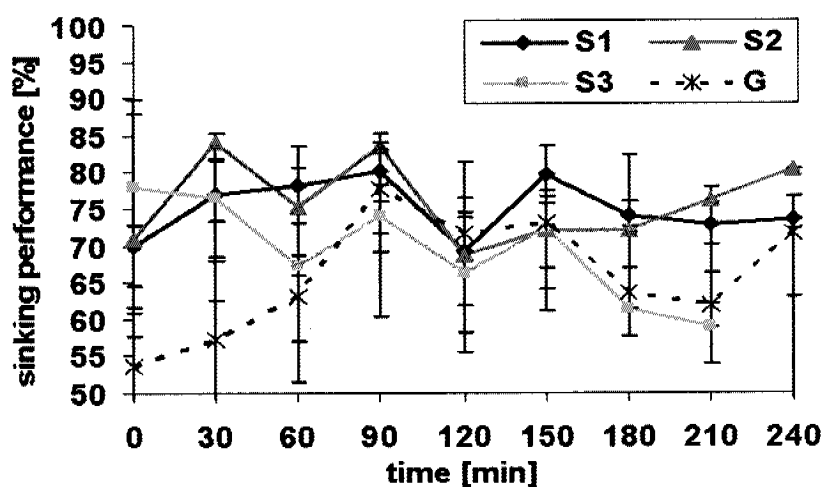
### Influence of test meal composition

Volunteers were asked to eat the meal within 15 min. Immediately after completion of the meal, the marked floating tablet was ingested together with 50 ml of water. Subsequently, each volunteer was placed in sitting position in the 0.5 T open configuration MRI system (Signa SP, GE Medical Systems, Milwaukee, WI) as shown in Figure 2.13. A standard send-receive surface coil for abdominal MRI was wrapped around the upper abdomen of the volunteer for signal reception. MR measurements were taken at 30 min intervals for at least 180 min and at most up to 240 min. At each time point, a stack of 24 sagittal MRI images covering the total gastric region (volume scan) were acquired within three breath holds of 25 seconds using a  $T_1$ -weighted fast spoiled gradient echo (FSPGR) sequence (repetition time, 150 ms; echo time, 8 ms; flip angle, 60°; field of view, 280 mm; slice thickness, 8 mm; interslice gap, 0 mm; matrix, 256 $\times$ 160). The volunteers were not allowed to drink or eat during the four-hour study period. However, they were allowed to move freely between the measurements.

	Meal composition	Weight (g)	Fat (g)	Energy (kcal)
Hamburger meal	Hamburger	130	15.6	250.9
	French Fries	160	20.8	448
	Green beans	120	0	42
	Orange juice	100	0	45
	Water	300	0	0
	Fruit salad	200	0	136
	<b>Total</b>	<b>1010</b>	<b>36.4</b>	<b>921.9</b>
Cheese meal	Camembert	40	13.4	153.2
	Curd cheese	90	14.4	189
	Whipped cream	20	4.44	51.4
	Potatoes	200	0	160
	Orange juice	100	0	45
	Water	300	0	0
	Fruit salad	200	0	136
	<b>Total</b>	<b>950</b>	<b>32.24</b>	<b>734.6</b>
Pasta Meal	Pasta	150	0	211.5
	Minced meat	120	14.4	231.6
	Olive oil	20	20	176.8
	Onions	100	0	38
	Tomatoes	300	0	96
	Orange juice	100	0	45
	Water	300	0	0
	<b>Total</b>	<b>1290</b>	<b>34.4</b>	<b>934.9</b>

Table 2.4: Composition of the test meals

a.



b.

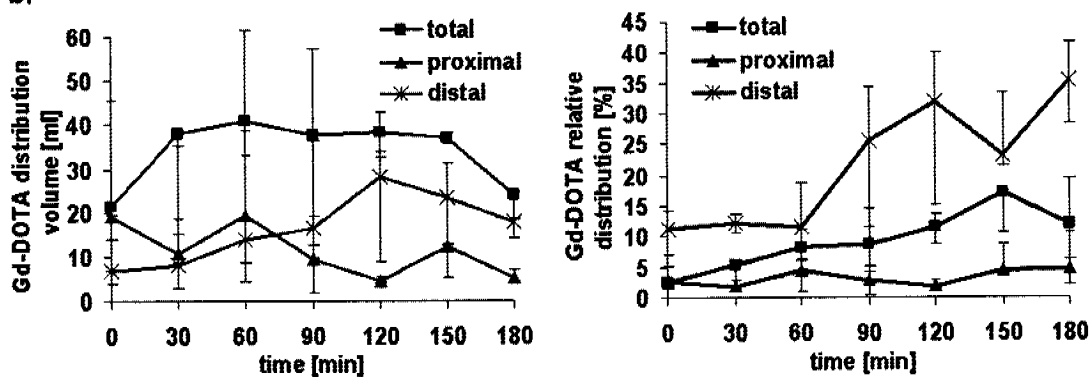
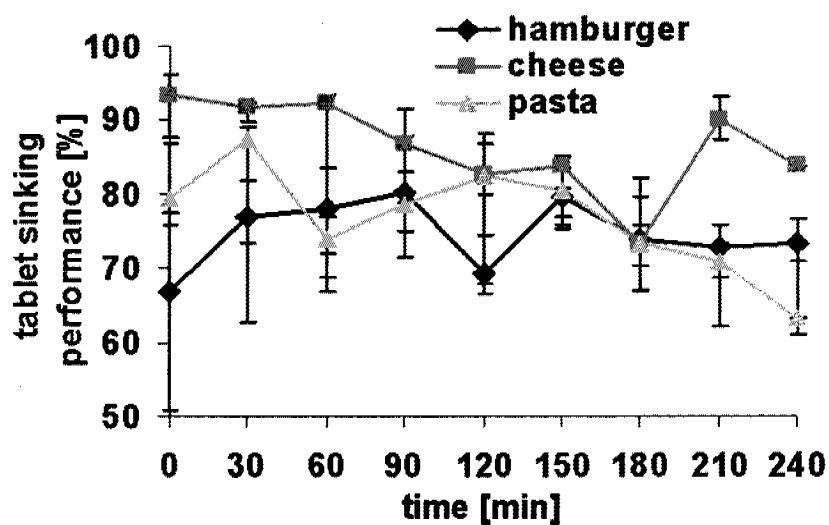


Figure 2.22: (a) Tablet sinking performance in % over 240 min study period for the four tablets  $S_{1-3}$  and G. (b) Absolute (ml) and relative (%) Gd-DOTA distribution volumes over 180 min study period in the total, proximal and distal stomach for tablet G.

a.



b.

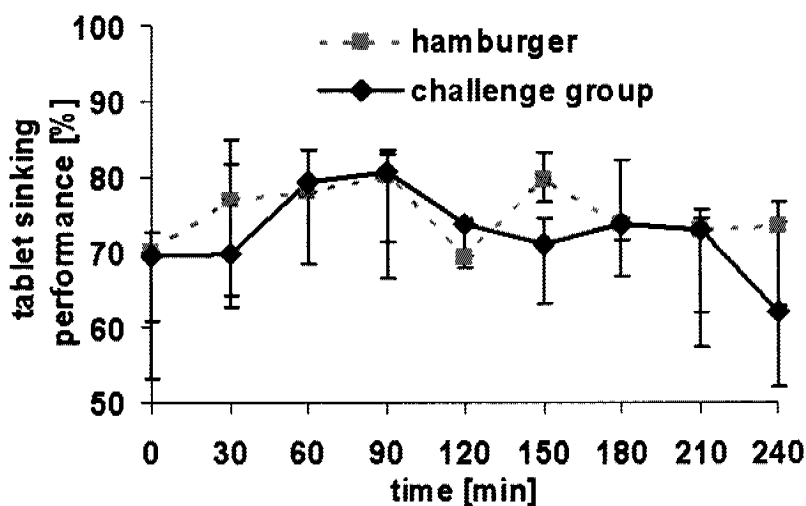


Figure 2.23: (a) Tablet sinking performance in % over 240 min for the three meal groups (hamburger, cheese, pasta). There was no difference in sinking performance despite faster emptying of the cheese meal. (b) Tablet floating performance in % over 240 min for the challenge group (solid line) and the corresponding hamburger group from study phase 1 (dotted line).

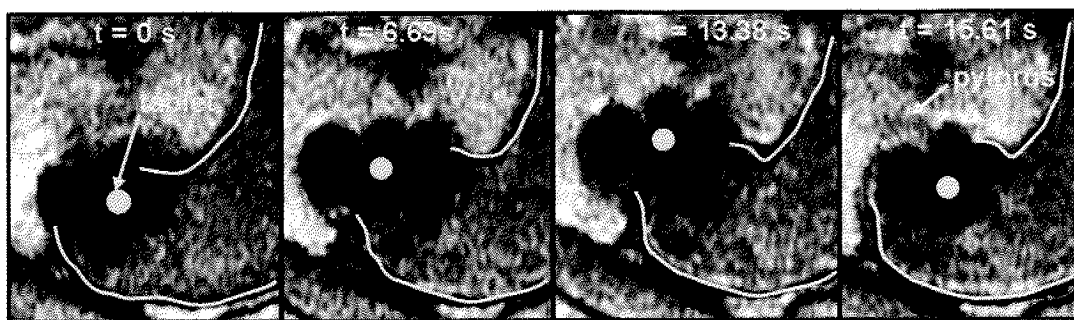


Figure 2.24: Four discrete time points ( $t = 0.0, 6.69, 13.38$  and  $15.61$  s) from a time series of an oblique coronal MRI image plane of a motility scan. Tablet, antral wall and pylorus are indicated in the images. The images show the repulsion of the sinking tablet into the antral cavity after reaching the vicinity of the pyloric sphincter. The tablet was slowly transported distally during a time period of  $14$  s and then quickly retropelled (within  $2.3$  s) into the stomach. The distance of tablet movement (back and forth) was approx.  $2\text{--}2.5$  cm. The location of the pylorus was not detectable on each motility image due to the MR signal distortion and resulting image artifact created by the nearby  $\text{Fe}_3\text{O}_4$  marked tablet. In this example, the pylorus is only clearly visible in the MRI image of time  $t = 15.61$  s.

of intragastric tablet performance and residence time.

The evaluation of the different sinking tablet formulations  $S_{1-3}$  indicated that tablet size was the determining factor for the prolonged gastric residence time. Although the three formulations showed comparable intragastric sinking performance, the smallest sized tablet  $S_3$  (density:  $1.34$  g/ml; diameter:  $6.9$  mm) never remained inside the stomach for the required period of time. This is supported by the observed properties of tablet  $G$  which showed reduced sinking performance (especially at the beginning and towards the end) but had similar tablet residence times as tablet  $S_1$  (density:  $1.3$  g/ml; diameter:  $8.8$  mm). These findings are consistent with results from Timmermans et al.<sup>129,133</sup> showing that in the upright seated position the diametral size of non-floating (NF) single units was the main intrinsic factor determining gastric retention time. Small size NF units (density:  $1.105$  g/ml; diameter:  $4.8$  mm) emptied first followed by medium (density:  $1.14$  g/ml; diameter:  $7.5$  mm) and then large size (density:  $1.24$  g/ml; diameter:  $9.9$  mm) units. This retention by size effect also observed in the current study was further supported by the acquired MRI motility movies. These nicely visualized the frequent retropelling of tablet  $S_1$  near the pylorus due to occlusive antral peristaltic contractions. This way, in all but one volunteer (for tablet group  $S_1$  as well as challenge group), tablet  $S_1$  was not emptied from the stomach before the end of study period ( $240$  min). Astonishingly however, in the outliers the tablet was already expelled at time  $t = 0$  or  $t = 120$  min, respectively. Such unexpected and unwanted variability in gastric retention time, frequently reported for sinking dosage forms,<sup>134</sup> is generally explained by the biological variation in the diameter of pyloric opening that can range from  $4$  mm up to  $10$  mm.<sup>135</sup> This early tablet emptying may also be due to different motility pattern. However, the MRI motility movies from the current study indicated similar peristaltic characteristics (for the hamburger meal)



between volunteers. Moreover, the detected peristaltic frequency of approx. 3/min and the low inter-individual variation in motility patterns was consistent with results from other MRI studies.<sup>40, 125</sup>

Due to the sinking characteristics of tablet *G*, the relative intragastric distribution of the released drug model (*Gd*-DOTA) was expected to become higher in the distal compared to the proximal stomach. However, the difference in relative drug model distribution volume only showed a statistical trend but no significance. The reduced sinking performance of this tablet and thus the increased proximal drug model volume could partially explain this finding. Another cause however was the restricted spatial distribution of *Gd*-DOTA within the distal meal volume (only 11–35%) as presented in Figure 3b. These rather low distal distribution volumes were likely to be due to concurrent meal (mixed with drug model) emptying from the distal stomach, however may also be amplified by the limited sensitivity of the MRI measurement to very low concentrations of *Gd*-DOTA. Latter cause would result in an underestimation of the actual distribution volume, whereas the first one might be of physiological relevance for the effectiveness of nutrient specific drugs. For example, drugs that must either bind to specific macronutrient or need to be emptied together with those, the exact rate of nutrient emptying must be considered in order to determine the appropriate release rate for the applied formulation. In the current study, it is very likely that both phenomena were active; their relative contribution however was not analysed.

The evaluation of possible meal dependent intragastric tablet properties showed that intragastric sinking performance was independent of meal composition. Gastric residence time was slightly reduced for the tablets administered with the cheese meal. Since the cheese meal had lower caloric contents compared to the other meals, above finding went together with a faster gastric emptying and suggested an effect of the meal emptying rate on tablet residence time. However, no correlation was found for the two parameters. It might have been the lower viscosity of the cheese meal that favored the earlier emptying of the tablet from the stomach.

No influence of the time point of administration on intragastric tablet performance was found. Sinking performance and residence time were similar for tablet administration after total (challenge group) or first quarter of total meal intake. Already at the first measurement time point  $t = 0$  min (max. 5 min after total meal intake) tablets from the challenge group showed similar intragastric position. For patients, this presents a very convenient tablet property, since it offers some (although limited) flexibility in medication handling.

Comparing the performance of the sinking tablets with our previous results on floating tablet formulations<sup>33</sup> it is noticeable that floating tablets exhibited longer gastric residence times despite smaller tablet size (tool size: 15 mm  $\times$  6.9 mm). Previous test meals and gastric emptying times were the same as for this study. This observation again confirms results from Timmermans et al.<sup>133</sup> showing that for seated body position, the size (within the range analysed in this study) has less influence on the gastric retention time for floating then sinking dosage forms.

Extensive investigation of in vivo properties of slow-release, gastric-retentive tablets, requires very time consuming study protocols. The herein presented experimental set-up permitted volunteers to move freely in between MRI measurements which is essential for a four-hour study period. However, volunteers were not allowed to lie down to prevent misinterpretation of results due possible effects of body position.<sup>43</sup> Using an open-configuration

MRI system allowed the in vivo analysis in the physiological seated position. In this body position, gravitational forces are usually directed from the proximal to the distal stomach volume and sinking tablet position is predictable. Although, posture might not be as critical for sinking as for floating tablets (except for the right lateral side), fair comparison between the two dosage forms was only feasible in the upright, seated position.

The experimental results of our study lead us to the conclusions that first, the gastroretention of sinking tablets is closely related to their overall size and second, a density of 1.3 g/ml is not sufficient to achieve a full sinking performance. In the presence of food, large and heavy tablets (1 g, size 19 mm x 8.8 mm) are very likely to remain in the stomach for over 4 hours. However, there is no guarantee that they will do so, and exceptions exist. It shows that the full stomach might empty solid particles with a size larger than 6 mm. Monolytic dosage forms of this size can not be regarded as safe gastroretentive forms even in the presence of food.

## Acknowledgment

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## Chapter 3

# Magnetic Resonance Imaging for the analysis of human gastric motor function and emptying

### 3.1 The effects of posture on the physiology of gastric emptying: a magnetic resonance imaging study

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## Abstract

*Background:* Gastric contents empty from the stomach despite frequent changes in body position. The mechanism that maintains gastric emptying independent of position is poorly understood.

*Aim:* Effects of body position on gastric emptying and motor function following ingestion of a non-nutrient liquid meal were studied.

*Methods:* Twelve volunteers were investigated in seated position (SP) and upside-down position (UDP) after ingestion of 300 ml water. Magnetic resonance imaging provided a non-invasive assessment of gastric emptying and volumes, intragastric distribution, peristaltic function.

*Results:* Post-prandial volume response (gastric adaptation) was greater in UDP than SP (280 vs. 250 ml;  $P < 0.05$ ) and a marked difference in distal/proximal intragastric distribution between UDP and SP was present (7% vs. 40%;  $P < 0.01$ ). Gastric emptying time was similar but emptying pattern was linear in UDP and exponential in SP. Peristalsis was slower in UDP than SP ( $2.75$  vs.  $2.96 \text{ min}^{-1}$ ;  $P < 0.01$ ). There was a correlation between gastric adaptation and gastric emptying time in SP ( $r^2 = 0.46$ ) but not in UDP.

*Conclusion:* The rate of gastric emptying for water is maintained despite major changes in body position. This study suggests that gastric emptying is mainly driven by gastric tonic contraction (retraction force); however hydrostatic pressure dictates fluid emptying in SP.

**Key words:** gastric emptying; gastric motor function; intragastric distribution; intragastric air; magnetic resonance imaging; posture

## Introduction

After a liquid meal gastric contents usually empty from the stomach at a steady rate, maintaining the delivery of fluid and nutrient to the absorptive surface of the small bowel<sup>136</sup>(1) To be effective this process must continue despite major changes in body position. The effect of position on the rate and physiology of gastric emptying has been extensively investigated over the last 40 years using various measurement setups and techniques.<sup>41–45, 137–139</sup> Different methodologies produced conflicting results and hence several aspects of this complex homeostatic mechanism remain controversial. In particular it is unclear whether gastric emptying of liquids is driven by low-pressure tonic contractions of the stomach with the formation of a gastro-duodenal pressure gradient ('pressure-pump') or the action of propagating high-pressure waves ('peristaltic-pump').<sup>4</sup>

Studies using antro-duodenal manometry and concurrent duplex ultrasonography<sup>5, 140</sup> or magnetic resonance imaging (MRI),<sup>4</sup> respectively, have suggested that the 'pressure-pump' mechanism is important in the gastric emptying of fluids. However, these studies were all performed in the upright sitting or right-lateral positions with the antrum and duodenum in a dependent position in which the antro-duodenal pressure gradient (and buoyancy) favors transpyloric outflow. Thus this research could not clarify the relative importance of the 'pressure-pump' and the 'peristaltic-pump' during position change.

Gastric MRI provides unique advantages for the non-invasive, simultaneous assessment of gastric emptying and gastric motor function. Several MRI studies have validated the measurement of gastric accommodation, peristaltic activity, intragastric distribution and gastric emptying.<sup>15, 16, 18, 36, 38, 60, 66, 78, 125, 141, 142</sup> MRI appears to have many characteristics

of an 'ideal' investigation of gastrointestinal function<sup>20</sup> providing a detailed and quantitative assessment of gastrointestinal structure and function. The aim of the current study was to apply gastric MRI to the study of posture on the rate and physiology of gastric emptying. A non-nutrient liquid (water) was used to avoid possible confounding by feedback inhibition from intestinal chemo-receptors. An open-configuration MRI system allowed the non-invasive measurement of gastric physiology in the upright, seated and upside-down position for the first time. These radically different positions were chosen to provide the clearest possible demonstration of whether different mechanisms of gastric emptying were operating. We hypothesized that the upright, seated position would increase the gastro-duodenal hydrostatic pressure gradient and favor the 'pressure-pump' mechanism, whereas the upside-down position would require the 'peristaltic-pump' to force the liquid against the pressure gradient and through the empty antrum into the duodenum.

## Methods

The measurement protocol was approved by the local Institutional Review Board and the ethical committee of the University Hospital. Informed consent was obtained from all volunteers who participated in this study.

### MRI measurements

Twelve healthy volunteers of normal weight (10 males, 2 females; age, 24–34 years; BMI, 20.1–26.1 kg/m<sup>2</sup>) were investigated in an open configuration MRI system (Signa SP/i 0.5 T, GE Medical Systems, Milwaukee, WI, USA). The special architecture of this MRI system with a 56 cm wide gap between two vertically placed ring magnet components allowed imaging of volunteers in arbitrary body position. The investigations were performed consecutively first in the upright, seated position (SP) and then in the upside down-position (UDP) on the same study day. In UDP subjects rested on their shoulders while being supported from behind (3.1a). In this posture the long axis of the stomach was always at an angle steeper than 45° to the horizontal scanner table and the antrum was essentially filled with air (3.1b). The volunteers ingested 300 ml of water labeled with 0.5 mM *Gd*-DOTA (DOTAREM®, Laboratoire Guerbet, France) in the corresponding body position within 1 minute using a sports bottle to minimize spillage and air swallowing. Before and immediately after water intake a MRI "volume scan" covering the complete gastric region (details below) was acquired (3.2a). Further volume scans, each followed by dynamic "motility scan" sequences (details below), were performed every 5 min until 30 min. For the motility scans, one oblique coronal image plane was aligned with the long axis of the stomach such that the antrum lay always in this plane. In this way the propagating gastric contraction waves could be followed over time (3.2b). After gastric emptying in SP was complete the UDP was assumed and the process was repeated.

A fast spoiled gradient echo (FSPGR) sequence and a standard abdominal surface coil was applied for image acquisition. For the volume scan: 20 sagittal image slices; T<sub>scan</sub> = 44 s (during 2 breath holds); TR/TE = 17/8 ms, flip angle = 60°; Δz = 10 mm; matrix, 256×160; FOV=350 mm; RFOV=0.75. For the motility scan: 50 - 70 dynamics; oblique coronal image slice; T<sub>scan</sub> = 79–148 s (during gentle breathing); TR/TE = 17/8 ms or 13/6 ms; flip angle = 60°; Δz = 10 mm; matrix, 256×160; FOV=350 mm; RFOV=0.75)

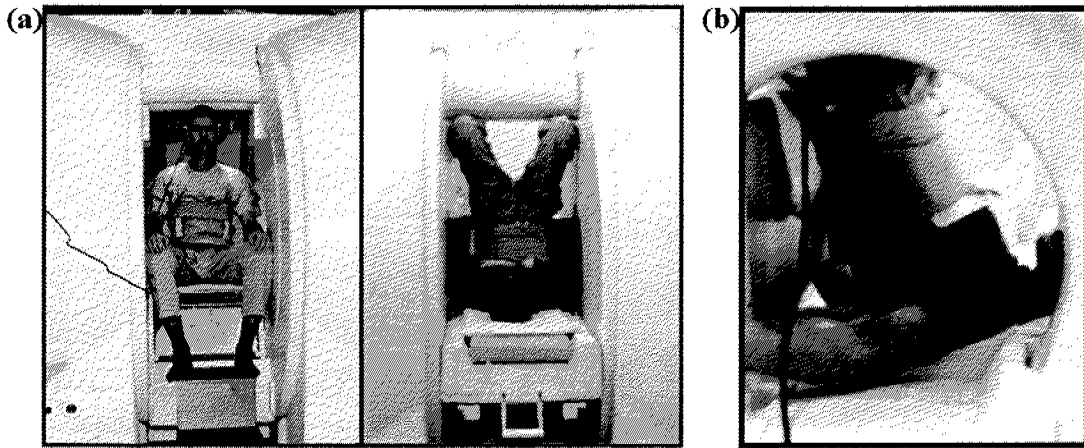


Figure 3.1: (a) The 0.5 T open configuration MRI system with a volunteer in SP (left) and UDP (right). (b) In UDP the long axis of the stomach was always at an angle steeper than  $45^\circ$  to the horizontal scanner table. The standard abdominal surface coil was fixed around the subject's abdomen.

with images recorded every 1.6 to 2.1 seconds

### Data analysis

Fasted and post-prandial total stomach volume and meal volume (labeled water) were outlined for each volume scan using a semi-automatic segmentation method. Gastric air made up the difference between total stomach and meal volume. In addition the stomach was divided into proximal and distal compartments based on the three-dimensional (3D) plot of stomach contours (3.3a). Total, proximal and distal stomach volumes, meal volumes and gastric air volumes were plotted over time to generate "volume curves". The primary outcome measures were fasted and initial post-prandial gastric volumes, gastric relaxation, gastric emptying halftime ( $t_{1/2}$ ) of the meal in SP and UDP and an assessment of intragastric water distribution between the proximal and distal stomach over time. Secondary analyses included measurement of gastric peristalsis and changes in total post-prandial stomach and gastric air volume. Gastric air volume was analyzed because it contributes to stomach volume and may affect intragastric pressure and gastric tone (and thus gastric emptying).

Gastric relaxation was defined as the volume difference between the initial post-prandial ( $t = 0$  min) and fasted ( $t = -2$  min) stomach volume. Gastric emptying was defined as the change in meal volume over time. The relative intragastric distribution was defined as the ratio of distal to proximal water volume in percentage. By convention volume measurements were normalized to the volume immediately after meal ingestion and expressed as a percentage. This transformation reduces inter-individual variation and facilitates statistical comparison. The normalized gastric emptying data was plotted for each subject and gastric emptying halftime ( $t_{1/2}$ ) was calculated for total meal emptying. For both positions, a linear and exponential regression was fitted to the gastric emptying data. The coefficients of the linear ( $r^2_{lin}$ ) and exponential ( $r^2_{exp}$ ) fit were calculated. In addition, the generated volume curves were statistically compared to analyze the effect of body

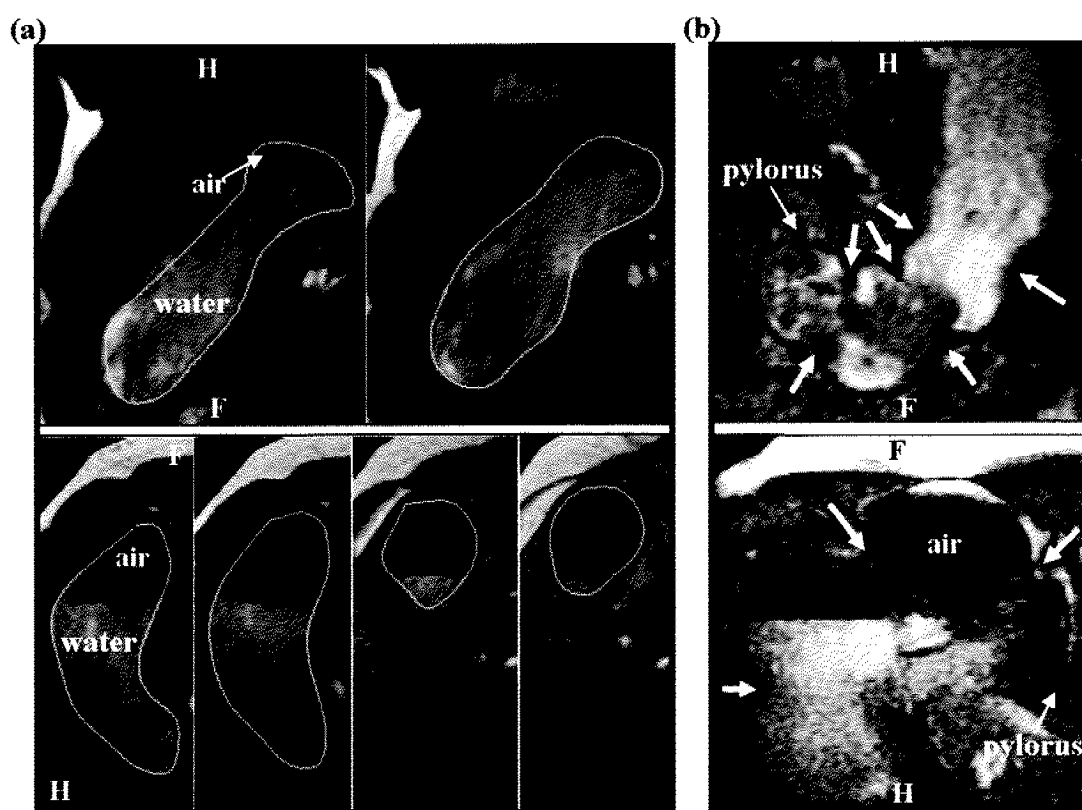


Figure 3.2: (a) Consecutive sagittal images of MRI volume scans from volunteer in SP (top) and UDP (bottom), respectively. Stomach contours are outlined in each image. The images demonstrate the prominent difference in intragastric meal (water) and air distribution (F: feet direction, H: head direction). (b) Oblique coronal images of motility scan from same volunteer in SP (top) and UDP (bottom). Peristaltic contraction waves (white arrows) and the position of the pylorus are indicated in the images. UDP motility image nicely depicts that gastric air was confined to the distal stomach in this position (F: feet direction, H: head direction).

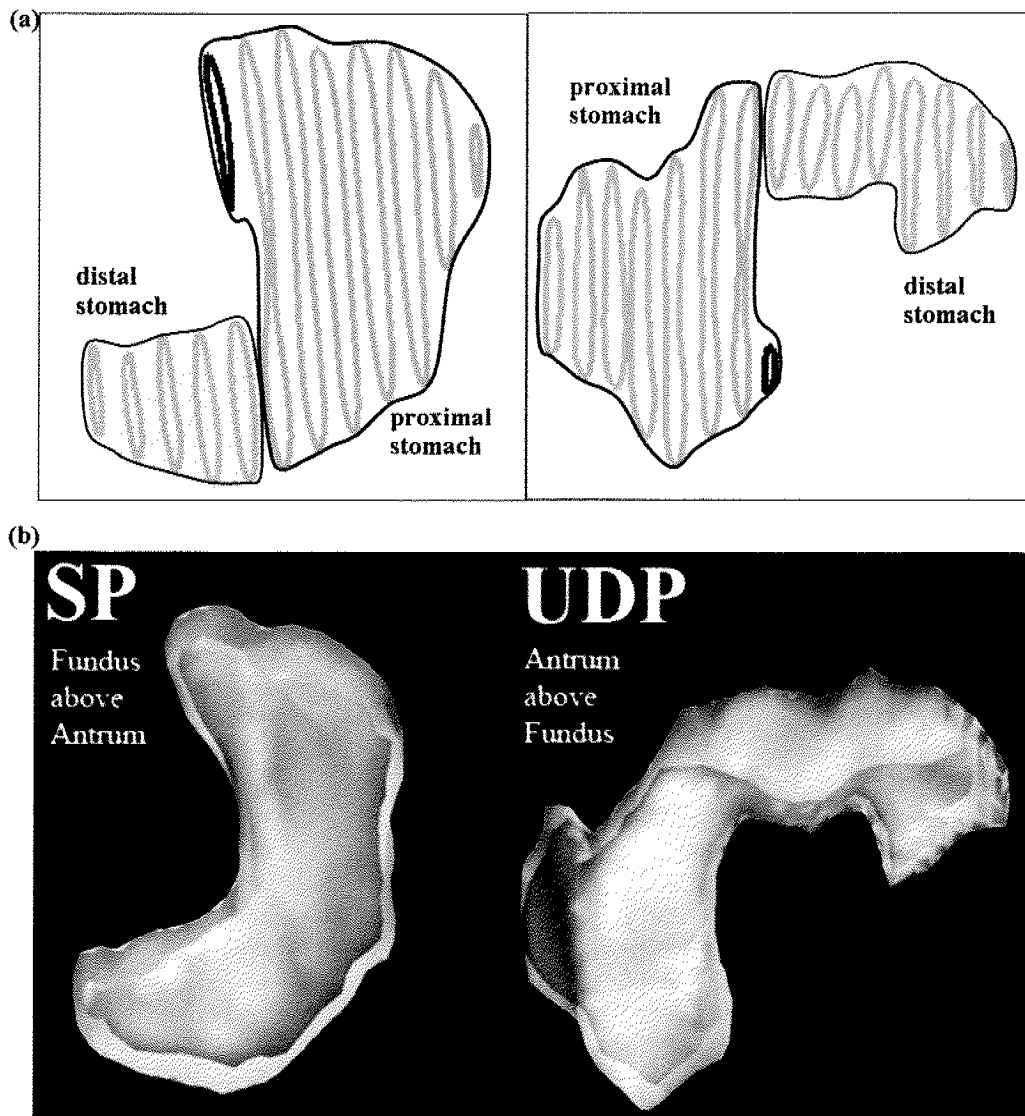


Figure 3.3: (a) 3D contour plot of initial post-prandial stomach volume of volunteer in SP (left) and UDP (right). The division into proximal and distal stomach volume is indicated. (b) Corresponding 3D visualizations of initial stomach (white) and meal (red) volumes. The meal volumes (red) were down-scaled to avoid overlap of rendered surfaces. The 3D representation was performed to provide qualitative information on intragastric distribution and stomach shape.

position and time on the total stomach, meal and gastric air volume.

Peristalsis (phasic motility) was assessed as the average frequency of all detected propagating contraction waves in a volunteer, now referred to as peristaltic activity. In addition, the average frequency within each 5 min interval was plotted over time<sup>125,141</sup> to generate a “frequency curve”.



## Statistics

Data were not normally distributed and were expressed as the median (interquartile range). By convention, in the figures the data is presented as mean ( $\pm$  SD). In four subjects, measurements could not be performed at time  $t = 30$  min. The last observation carried forward (LOCF) approach was used to fill the missing data points. The primary outcome measurements as well as peristaltic activity from the SP and UDP were statistically compared using the Wilcoxon matched pairs test. A two-way (body position and time) repeated measures ANOVA with Greenhouse-Geisser correction was used to analysis the volume curves and determine the influence of body position and time on the peristaltic frequency and the stomach, meal and gastric air volumes (secondary outcome measures). Analysing the interaction between body position and time allows assessing differences in the characteristics (dynamics) of the volume curves between the two positions. A  $P$  value of  $< 0.05$  was considered to be significant. Data were not normally distributed and were expressed as the median (interquartile range). By convention, in the figures the data is presented as mean ( $\pm$  SD). The primary outcome measurements as well as peristaltic activity from the SP and UDP were statistically compared using the Wilcoxon matched pairs test. Dynamics and amplitude of gastric emptying, peristaltic frequency, stomach and gastric air volumes were compared using General Linear Model (GLM) repeated measures with Greenhouse-Geisser correction. In four subjects, measurements could not be performed at time  $t = 30$  min. The last observation carried forward (LOCF) approach was used to fill the missing data points. A  $P$  value of  $< 0.05$  was considered to be significant.

## Results

Image acquisition and analysis was successful in all subjects. Fasted and post-prandial stomach volumes and meal volumes were detected and outlined in SP and UDP and 3D visualization of the stomach was performed (3.3b).

### Fasted and initial post-prandial volumes

Gastric volumes in the fasted and initial post-prandial condition as well as gastric relaxation and the difference between fasted and initial post-prandial gastric air volume are listed in table 3.1. Although fasted stomach volume and meal volume, i.e. residual gastric were not different in both positions, fasted gastric air volume was slightly larger for SP. After water ingestion meal volume was similar, but initial total stomach volume showed a trend for a larger volume in UDP. This difference was due to a pronounced difference for initial gastric air volume. Gastric relaxation (GR) as well as the difference between fasted and initial post-prandial gastric air volume (AD) was larger for UDP. In both positions stomach volume was greatest immediately after meal ingestion. For SP, the correlation between initial post-prandial stomach volume and gastric emptying halftime was ( $r^2 = 0.47$ ).

	SP		UDP	
	fasted	after water	fasted	after water
SV (ml)	122 (103 - 149)	377 (345 - 401)†	101 (81 - 142)	417 (359 - 458)†
MV (ml)	28 (18 - 54)	296 (279 - 323)	40 (0 - 75)	290 (258 - 323)
AV (ml)	89 (62 - 113)*	64 (53 - 93)‡	75 (51 - 82)*	123 (80 - 140)‡
GR (ml)	-	250 (219 - 271)*	-	280 (255 - 338)*
AD (ml)	-	-16 (-44 - 10)‡	-	58 (31 - 82)‡

\* Significant difference with  $P < 0.05$  between SP and UDP.

† Trend for a difference with  $P = 0.06$  between SP and UDP.

‡ Significant difference with  $P < 0.01$  between SP and UDP.

Table 3.1: Stomach volume (SV), meal volume (MV) and intragastric air volume (AV) in the fasted condition and after ingestion of 300 ml of water in SP and UDP. Gastric relaxation (GR) and the difference between fasted and initial post-prandial air volume (AD) after ingestion for SP and UDP.

### Intragastric distribution

A marked difference in intragastric distribution was present between SP and UDP after meal ingestion; in SP gastric contents were approximately evenly distributed between the proximal and distal stomach, whereas almost all the ingested fluid was retained in the proximal stomach in UDP (distal: proximal ratio; SP: 40% (25/62%) vs. UDP: 7% (5/13%);  $P < 0.01$ ).

### Gastric emptying

Normalized gastric emptying data in SP and UDP is shown in 3.4a. Measurement error is low for MRI assessments of gastric volumes,<sup>143</sup> however there was a large inter-individual variation for the water emptying as denoted by the large standard deviations. No lag phase was observed and total stomach volume decreased with meal volume until emptying was complete. No significant difference was detected for  $t_{1/2}$  (SP: 15.8 min (11.5–17.0 min) vs. UDP: 18.3 min (13.8–19.3 min);  $P = 0.07$ ), and emptying was completed within 25 min in both positions. In SP the regression that provided the best fit to the gastric emptying data was exponential. In UDP the best fit was linear ( $r^2_{lin} = 0.96$  (0.95–0.98) vs.  $r^2_{exp} = 0.92$  (0.9–0.96);  $P < 0.05$ ). As shown in figure 4b, this difference was even more clearly demonstrated when the pattern of gastric emptying from the proximal and distal stomach was considered ( $P < 0.01$  for all comparisons). In SP water was retained in both the proximal and distal stomach; the meal emptied in an exponential fashion from the proximal and distal stomach (figure 4b, left). In UDP almost all the water was retained in the proximal stomach with only a minimal amount seen in the distal stomach; gastric contents emptied in a linear fashion from the proximal stomach whereas the (small) volume in the distal stomach remained constant (3.4b, right). These findings are reflected in the statistical analysis comparing the total, proximal and distal meal volume curves for SP and UDP. The analysis of the **total** volume curves showed a significant effect of time (decrease of both meal volumes) ( $F(2, 23) = 184$ ,  $P < 0.001$ ), a non-significant effect of body position (similar meal volumes) and a strong trend for a significant interaction between body position and time (tendency for different dynamics of the volume curves) for the first 20 min of the study period ( $F(3, 29) = 2.9$ ,  $P = 0.059$ ). The analysis of the **proximal** volume curves showed a significant effect of time ( $F(2, 22) = 177$ ,  $P < 0.001$ ), a significant effect of body position ( $F(1, 11) = 5.8$ ,  $P < 0.05$ ) and a non-significant interaction between body position and time for the complete study period. The analysis of the **distal** volume curves showed a significant effect of time ( $F(3, 33) = 33.8$ ,  $P < 0.001$ ), a significant effect of body position ( $F(1, 11) = 28.8$ ,  $P < 0.001$ ) and a significant interaction between body position and time ( $F(3, 28) = 18.2$ ,  $P < 0.001$ ) for the complete study period.

### Gastric peristalsis

Peristalsis was observed in all subjects in both positions. The degree of occlusion increased as the peristaltic wave progressed along the long axis of the stomach and complete occlusion was present in the distal antrum. Peristaltic activity was different for SP and UDP with a higher average frequency of propagating contraction waves in SP (SP: 2.96 1/min (2.83–3.06) vs. UDP: 2.75 1/min (2.59–2.90);  $P < 0.01$ ). Peristaltic frequency (higher in SP) increased after the first 5 min interval and then remained constant until gastric emp-

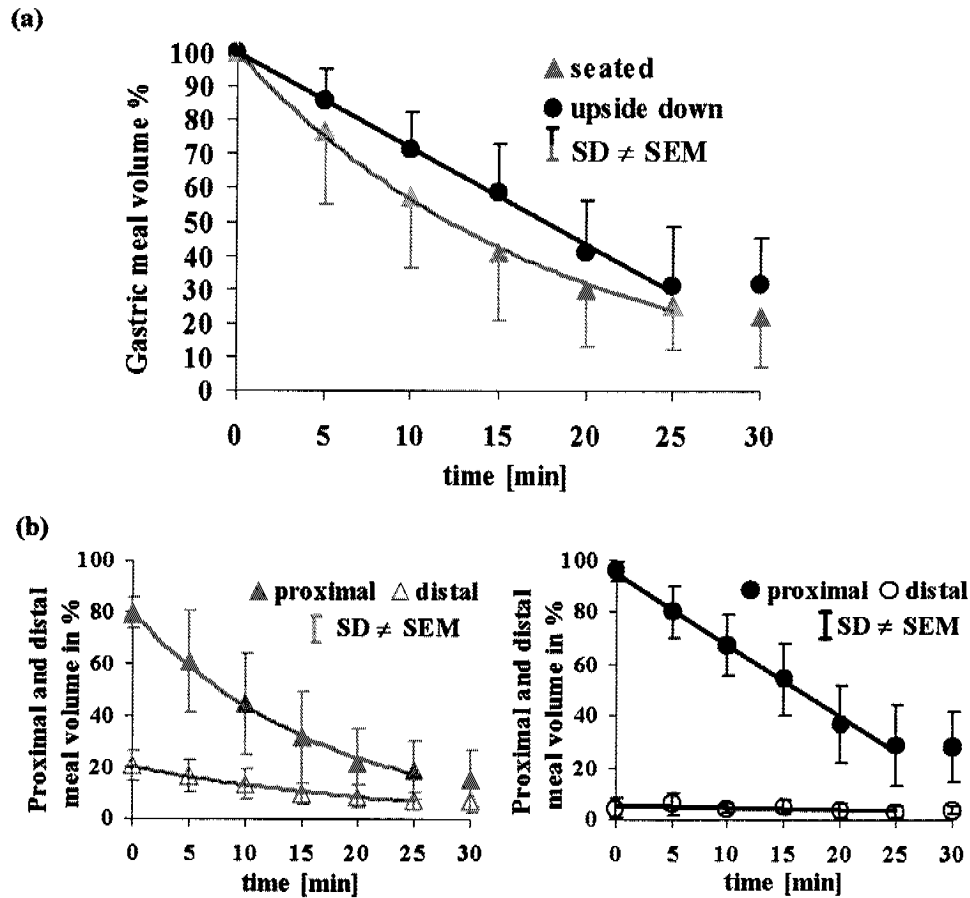


Figure 3.4: **(a)** Gastric emptying curves for SP and UDP. The regression was fitted to the first 25 minutes because negligible emptying occurred after this time (i.e. a small gastric residual was present). Measurement error of gastric volumes is low. The standard deviations provided reflect the large inter-individual variation of gastric emptying. **(b)** Proximal and distal meal volumes over the 30 min study period (expressed in percentage of the total meal volume) in SP (left) and UDP (right). In SP water was retained in both the proximal and distal stomach and emptied from both compartments in an exponential fashion. In UP almost all the water was retained in the proximal stomach with only a minimal amount seen in the distal stomach. The meal emptied in a linear fashion from the proximal stomach whereas the (small) volume in the distal stomach remained constant.

tying was complete ( $P < 0.01$ ). The findings are again reflected in the statistical analysis comparing the frequency curves for SP and UDP. There was a significant effect of time (initial frequency increase) ( $F(3, 30) = 12.4$ ,  $P < 0.001$ ), a significant effect of body position (higher frequency for SP) ( $F(1, 11) = 23.4$ ,  $P < 0.05$ ), but a non-significant interaction between body position and time (similar characteristics of the frequency curves) during the first 20 min of study period. No correlation was seen between peristaltic frequency and the rate of gastric emptying in either position.

### **Stomach and gastric air volume**

Comparing the volume curves of the total stomach for SP and RP, a significant effect of time (decrease in volume) ( $F(2, 25) = 155$ ,  $P < 0.001$ ), no effect of body position (similar volumes) and no interaction of body position and time (similar dynamics) was observed (figure 5a). Gastric air volume was larger initially in UDP and emptied from the stomach within the first 15 min (in all but two volunteers). This is clearly reflected in the statistical analysis comparing the gastric air volumes curves for SP and RP. The comparison over the first 20 min showed a significant effect of time ( $F(2, 20) = 4.5$ ,  $P < 0.05$ ), a significant effect of body position ( $F(1, 11) = 6.6$ ,  $P = 0.05$ ) and a significant interaction between body position and time ( $F(2, 23) = 6.1$ ,  $P < 0.01$ ) (figure 5b). Consequently, for UDP, there was a significant interaction between body position and time (different dynamics of volume curves) between the meal and stomach volume ( $F(3, 28) = 7.7$ ,  $P = 0.001$ ). In SP, no common pattern for the change of air volume was observed and stomach volume curves showed similar characteristics.

## **Discussion**

This study shows that posture has important effects on the physiology of gastric emptying for a non-nutrient liquid. The intragastric distribution of gastric contents was radically altered by moving from the upright, seated position (SP) to the upside-down position (UDP). The distal stomach (antrum) was always filled with liquid in SP, whereas the proximal stomach (fundus) retained almost all the gastric content in UDP. Thus, in SP passive forces (gravity and buoyancy) favored the flow of liquid through the pylorus, whereas in UDP these factors acted against gastric emptying. Despite this fundamental change in the direction of forces, the rate of gastric emptying was similar in both positions.

In the fasted condition a difference for SP and UDP was observed only for gastric air volume. The smaller fasted air volume in UDP probably reflected higher intra-abdominal pressure due to the higher abdominal wall tension needed to maintain this strenuous position. After ingestion of the test meal, post-prandial meal volume was similar in both positions however gastric volume response (gastric relaxation), was greater in UDP due to the increase in gastric air volume in this position. The cause of this larger volume response may not be explicitly derived without additional intra-luminal pressure information. The increase in initial gastric air volume for UDP could either suggest a larger relaxation of the stomach or more retained air in the stomach for this position. A posture dependent decrease in vagal stimulation and thus decreased gastric tone favors the former hypothesis,<sup>144, 145</sup> whereas the altered intragastric meal distribution in UDP, preventing air to be belched, and the continuous emptying of gastric air supports latter hypothesis.

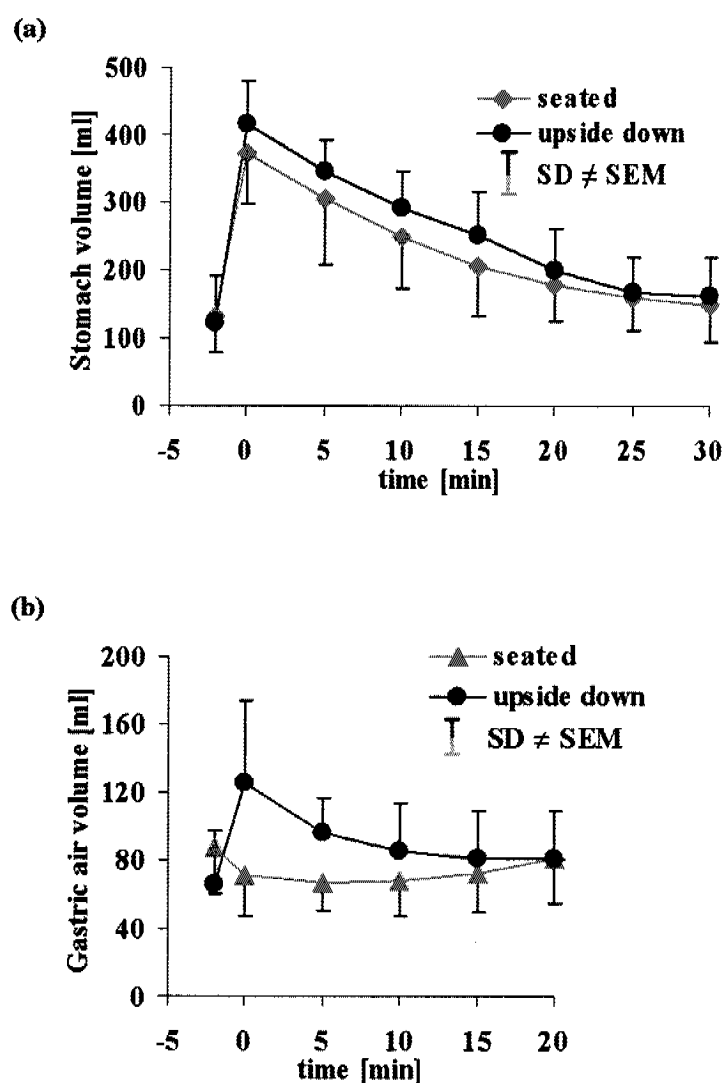


Figure 3.5: **(a)** Total stomach volume in fasted state ( $t = -2$  min) and over 30 min postprandial for SP and UDP. Similar dynamics were observed for the stomach volume curves despite a difference in the emptying dynamics. **(b)** Intra-gastric air in fasted state ( $t = -2$  min) and during the first 20 min of gastric emptying. After the initial increase in gastric air volume in UDP, the air was continuously emptied into the small intestine within 15 min.

Changes in gastric peristalsis were seen with position. MRI motility scans revealed an initial increase in peristaltic frequency for both positions and a small reduction in peristaltic frequency in UDP compared to SP during gastric emptying. The reduced frequency may be a consequence of increased vagal activity in UDP. Interestingly, this initial increase in frequency was also observed in another study for different nutrient liquids<sup>77</sup> and supports the hypothesis of an existent initial postprandial regulation (adaptation) phase for gastric motor activity. No correlation between peristaltic frequency and gastric emptying was found for SP as well as UDP. Additionally, the change in peristaltic frequency did not explain the difference in gastric emptying pattern between the two positions. The force of contraction cannot be assessed non-invasively; however the occlusion of the distal stomach by propagating waves was similar in both positions. These findings suggest that peristalsis was not the primary force that drives gastric emptying in *both* positions. This complies with results of recently performed studies showing that most fluid emptying occurs during periods of relative quiescence in antral and duodenal peristaltic activity.<sup>4,5</sup>

Gastric tonic motility modulates intragastric pressure and thus the gastroduodenal pressure difference.<sup>146</sup> In SP, for a liquid meal, the gastroduodenal pressure gradient is determined by the initial hydrostatic pressure of the ingested liquid (determined by volume ingested and stomach shape) and the retraction force (continuous tonic contraction) of the stomach. The exponential dynamics of stomach and meal volume during emptying (with constant air volume) in SP favor the hypothesis of a mainly hydrostatic pressure driven emptying process. In Theory, applying Torricelli's Law,<sup>147</sup> the change in liquid volume over time ( $V(t)$ ) for hydrostatic pressure driven emptying must follow the function:  $V(t) = (a - bt)^2$ , with time  $t = [0, \frac{a}{b}]$ ,  $a^2$  = initial water volume ( $V(0) \leq 300\text{ml}$ ) and  $b \leq \frac{\sqrt{V(0)}}{t_{\text{empty}}}$ . This function closely resembles an exponential function ( $V(t) = ae^{-bt}$ ,  $a = V(0)$ ,  $b \leq \frac{\ln(2)}{t_{1/2}}$ ) for the given time period. Deviations from the quadratic function to a more linear pattern can only be attributed to the concurrently acting gastric retraction force. This conclusion is obvious since a linear emptying pattern would only be produced by a constant intragastric liquid level (hydrostatic pressure) which must be maintained by continuous gastric tonic contraction.

Linear gastric emptying pattern was present in UDP, a position in which the effects of hydrostatic pressure operate against gastric emptying. Thus, this emptying pattern must have been mainly produced by active gastric contraction. As presented in figure 3.5a, stomach volume decreased continuously over time (especially the proximal volume) due to gastric tonic contraction (retraction force), providing a constant delivery of water into the distal antrum where it was emptied from the stomach. The presence of a positive gastroduodenal pressure gradient is evidenced by the finding that gastric air also emptied continuously (and fast) from the stomach into the small bowel (figure 3.5b). This rapid emptying of gastric air explains the non-significant effect of body position on the stomach volume (when analyzed for the complete study period) for SP and RP, despite the volume difference observed for the initial postprandial time point. Although gastric emptying time and peristaltic frequency were uncorrelated, it cannot be excluded that peristaltic contraction waves contributed to gastric emptying in both positions. If present, this process may be of particular importance in UDP aiding the distal transport of gastric contents against the effects of gravity.

Although a non-nutrient liquid was administered to avoid intestinal feedback from chemo-

receptors, pyloric regulatory mechanisms can not be excluded in the control of water emptying. In SP, with the duodenum in a dependent position, increased pyloric resistance initiated by feedback from duodenal mechanoreceptors stimulated by duodenal distension may inhibit rapid water emptying.<sup>148</sup> In UDP, this control mechanism was probably ineffective. In the recent study, due to the non-invasive study design no concurrent intraluminal manometry recordings were performed to test this hypothesis.

It must be mentioned that an emptying study with nutrient liquids would be impracticable with the presented measurement set-up. The shown upside down body position for volunteers to remain in, which was predetermined by the MRI system architecture (see figure 3.1), limited the study duration to a maximum of 30 min. However, in principle, such MRI emptying studies are feasible by using a specially designed MRI system (Upright<sup>TM</sup> MRI system, FONAR Corporation, Melville, NY USA).

The insights into gastric physiology provided by this study are the result of developments in gastric MRI. This technology provides a comprehensive description of gastric function by simultaneously detecting gastric emptying and gastric tonic and peristaltic motor function, and uniquely the assessment of intragastric distribution of gastric contents. This study demonstrates vividly the value of MRI as a non-invasive investigation of gastrointestinal structure and function.

In conclusion the stomach maintains the rate of gastric emptying for a non-nutrient fluid despite major changes in body position and intragastric distribution of gastric contents. In SP and UDP the rate of gastric emptying was driven by gastric tonic contraction. The exponential (or quadratic) gastric emptying pattern observed for SP was dictated by the contribution of hydrostatic pressure to the emptying process. In UDP, where hydrostatic pressure acted against gastric emptying the dynamics of the linear gastric emptying pattern was likely due to continuous gastric tonic contraction maintaining a constant gastro-duodenal pressure gradient. These findings provide further support to the hypothesis that the stomach rather resembles a ‘pressure pump’ than a ‘peristaltic pump’.

## Acknowledgment

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## 3.2 Gastric motor function and emptying in the right decubitus and seated body position as assessed by magnetic resonance imaging

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## Abstract

*Purpose:* Using MRI to determine the effect of right decubitus lying body position on relevant parameters of human gastric function in healthy volunteers.

*Materials and methods:* Post-prandial gastric function after ingestion of a solid/liquid meal was assessed over 90 min in right decubitus (RP) and seated (SP) body position. 10 healthy volunteers were imaged using two MRI systems of different architecture and field strength. Intra-individual comparison of stomach and intragastric air volume, intragastric meal distribution, gastric emptying, and gastric peristalsis was performed.

*Results:* There was no difference in gastric relaxation (RP, 372 ml vs. SP, 384 ml) and initial gastric volumes (stomach: RP, 458 ml vs. SP, 462 ml; meal: RP, 377 ml vs. SP, 399 ml; intragastric air: RP, 110 ml vs. SP, 98 ml). Post-prandial stomach volume and gastric activity was similar (RP and SP,  $3.1 \text{ min}^{-1}$ ). Meal emptying showed different characteristics resulting in a significant however small difference in meal volume at  $t = 90 \text{ min}$  (RP, 229 ml vs. SP, 252 ml;  $P < 0.05$ ).

*Conclusion:* Gastric MRI in RP is feasible for GI clinical research on gastric motor function. The subtle difference in meal emptying may be induced by posture dependent vagal activity. This study confirms MRI as highly sensitive imaging technique for the assessment of GI function in humans.

**Key words:** magnetic resonance imaging, body position, gastric emptying, intragastric distribution, gastric peristalsis, gastric relaxation

## Introduction

In recent years, magnetic resonance imaging (MRI) has been established as a valuable technique in human gastrointestinal (GI) research for the analysis of gastric function.<sup>15,16,37,60</sup> Because of its various advantages over radionuclide and ultrasound imaging methods MRI represents an ideal technique for the direct assessment of GI physiology<sup>20</sup> and thus will play an important role in GI research and clinical diagnosis in the future.<sup>17,51</sup> Modern high-field MRI systems have horizontally aligned whole-body architecture only allowing measurements of organ function in the lying body position. This may present a limitation for gastric MRI, since several studies using  $\gamma$ -scintigraphy and intra-luminal manometry have shown that posture may influence gastric function. In these studies, gastric emptying rate of liquids as well as solid/liquid meals and number of antropyloric contraction waves was different for lying compared to upright seated position.<sup>41–45</sup> However, due to the very different measurement principles (radioactive decay vs. hydrostatic pressure vs. magnetic resonance), scintigraphy and manometry data are not directly comparable to data derived using MRI. Furthermore, compared to MRI,  $\gamma$ -scintigraphy and intra-luminal manometry are not feasible to simultaneously assess data on gastric emptying, stomach volume, intragastric meal distribution and gastric peristalsis. To evaluate gastric MRI for the use in clinical research and diagnosis of GI pathophysiology it is inevitable to investigate post-prandial gastric function in the lying body position and detect differences to the upright, seated position.

The aim of the present study was using MRI to determine the effect of right decubitus lying body position on relevant parameters of human gastric motor function in healthy volunteers. Imaging protocols were developed for two MRI systems of different architecture allowing intra-individual comparison of stomach and intragastric air volume, intragastric

meal distribution, gastric emptying and gastric peristalsis between right decubitus (RP) and seated (SP) body position.

## Methods

### Subjects

Ten healthy volunteers (4 women, 6 men) with a mean age of 25.6 years (range 20–34 years) participated in this study. All subjects had no history of gastrointestinal disease and took no medication that affected gastric function. Written informed consent was obtained from each volunteer and the study protocol was approved by the local Ethics Committee.

### Study Protocol

Each volunteer was examined on two different study days in the right decubitus (RP) and seated (SP) body position respectively. When measurements were performed in the morning, volunteers were asked to arrive at the MR centre after an overnight fast. In case measurements were performed in the afternoon, volunteers were allowed to have a light and fat free breakfast at least 6 hours before MRI. On both study days, the same low fat solid/liquid test meal was administered. The solid phase consisted of 150 g cooked pasta (214.5 kcal; protein: 9 g; carbohydrates: 39 g; fat: 2.25 g) and the liquid phase of 150 ml of a nutrient drink (Ensure® Plus Drink, 225 kcal, protein: 9.375 g; carbohydrates: 30.3 g; fat: 7.38 g) labelled with 0.5 mM of the paramagnetic contrast agent *Gd*-DOTA (DOTAREM®, Laboratoire Guerbet, France). The solid meal was always administered prior to the liquid meal.

Measurements in RP were performed using the 1.5 T whole-body MRI system (1.5 T Intera, Philips Medical Systems, Best, The Netherlands) as shown in (3.6a). Volunteers ingested the solid meal in SP in the scanner room. Immediately after solid meal intake they were placed in RP inside the whole-body MRI system and ingested the liquid meal. Measurements in SP were performed using the 0.5 T open-configuration MRI system (Signa SP/i 0.5 T, GE Medical Systems, Milwaukee, WI, USA) as shown in (3.6b). Volunteers ingested both solid and liquid meal in SP inside the open-configuration MRI system.

A scan consisting of 20 sagittal image slices covering the complete gastric region (volume scan) was performed in fasted state ( $t = -15$  min) and after solid meal intake ( $t = -4$  min). After ingestion of liquid meal at time  $t = 0$  min volume scans followed by a dynamic scan sequence (motility scan) were performed in 5 min intervals until time  $t = 30$  min and thereafter in 10 min intervals until the end of the study period ( $t = 90$  min). Based on the preceding volume data, the image stack of the motility scan was positioned along the distal stomach axis in order to detect the propagating gastric contraction waves.

On the 1.5 T MRI system, steady state free precession (SSFP) sequences were used for imaging. For the motility scan the parallel imaging method SENSE<sup>149</sup>(13) was applied to increase image acquisition rate. Imaging parameters for this system were: *volume scan*: scan time = 15 s (breath hold),  $T_R/T_E = 4.6/2.3$  ms, FOV = 350 mm, slice thickness = 10 mm, image matrix = 256×205; *motility scan*: 3 parallel image slices each consisting of 120 dynamics, interleaved acquisition, scan time = 155 s (free breathing),  $T_R/T_E = 4.0/1.8$  ms, image matrix = 256×205, SENSE factor = 1.6). Rectangular parallel imaging

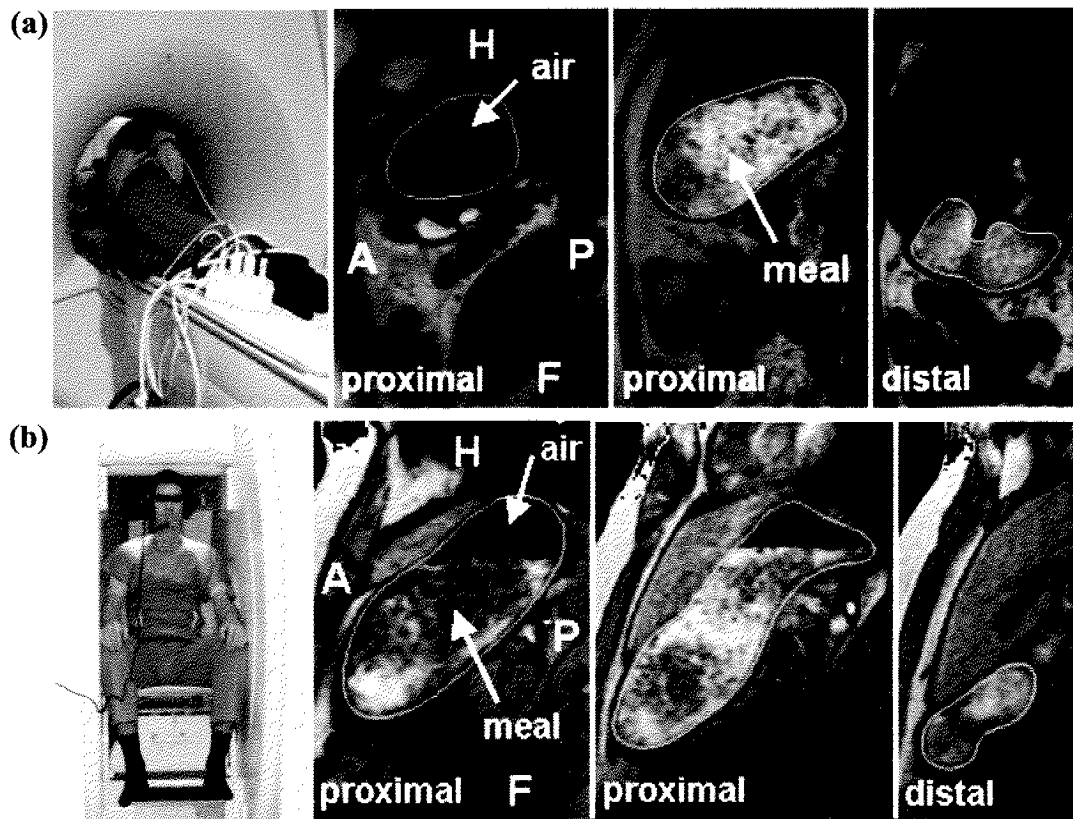


Figure 3.6: **(a)** Left: Volunteer lying in right decubitus body position inside the 1.5 T whole-body MRI system. Rectangular surface coils for parallel imaging were fixed around the abdomen. Right: Three sagittal MRI image slices (2 proximal, 1 distal) of a volume scan in RP with outlined stomach wall. Air and meal are indicated in the MRI images by arrows (F: feet, H: head, A: anterior, P: posterior). **(b)** Left: Volunteer sitting inside the 0.5 T open-configuration MRI system. A send-receive coil was fixed around the abdomen. Right: Three sagittal MRI image slices (2 proximal, 1 distal) of a volume scan in SP with outlined stomach wall. Air and meal are indicated in the MRI images by arrows (F: feet, H: head, A: anterior, P: posterior).

surface coils (height = 20 cm, width = 10 cm) were placed around the abdomen for signal detection.

On the 0.5 T MRI system, fast spoiled gradient echo (FSPGR) sequences were used for imaging. Imaging parameters for this system were: *volume scan*: scan time = 44 s (2 breath holds),  $T_R/T_E = 68/5.6$  ms, FOV = 350 mm, slice thickness = 10 mm, image matrix =  $256 \times 160$ ; *motility scan*: 50-70 oblique coronal dynamics, scan time = 109-148 s (free breathing),  $T_R/T_E = 12.5/5.6$  ms, image matrix =  $256 \times 160$ ). An abdominal send-receive coil was wrapped around the abdomen for signal detection.

### Image analysis

Total gastric area was outlined in each image of a volume scan. Based on this segmentation stomach volume, meal volume and intragastric meal distribution was determined over time. Stomach volume was calculated by summing the outlined pixels in each image slice and integrating the sum over all slices. In each image, meal contents could be identified by the distinct positive signal intensity compared to intragastric air. Summing the pixels reflecting meal contents and integrating the sum over all slices resulted in the meal volume. Intragastric air volume was determined by subtracting meal volume from stomach volume. A three-dimensional (3D) representation of the stomach based on the outlined contours was used to separate stomach volume into proximal and distal gastric volume (3.7). Stomach volume, total, proximal and distal meal volume and intragastric air volume (expressed in ml) was plotted over time. The complete study period of 90 min was divided in two phases, the ingestion phase (time points  $t = -15, -4, 0$  min) and the emptying phase (time points  $t = 0-90$  min). Furthermore, total emptying phase was sub-divided in early (0–30 min) and late (30–90 min) post-prandial period. Gastric relaxation was defined as the volume difference between stomach volume directly after and just before meal intake. Gastric relaxation was calculated after solid as well as after liquid meal ingestion. Gastric emptying was defined as the decrease of post-prandial meal volume over time. Gastric emptying curves defined as normalised remaining meal volume in the stomach were plotted over time. Intragastric meal distribution was defined as ratio of distal to proximal meal volume. Gastric peristalsis was analysed along a user defined distal stomach axis. Figure 3.8) shows in detail the analysis of the motility image data. Equally spaced profile lines were defined perpendicular to the axis (20 profiles in this example). The signal intensities along each profile of all dynamics were stacked and represented as “motility plot”. Frequency and velocity of gastric contraction waves were determined from these motility plots. Peristaltic frequency and velocity averaged over all time points was calculated. Gastric activity was defined as mean peristaltic frequency. Image analysis was performed using an in-house written software package implemented in IDL 5.5 (Research Systems Inc., Boulder, CO, USA).

### Statistical analysis

Data were analysed using SPSS® for Windows Release 11 software (SPSS Inc., Chicago, IL, USA). Logarithmic transformation was applied to stomach, meal and intragastric air volume to normalise data distribution. For four subjects in both RP and SP volume measurements at  $t = 90$  min could not be performed due to technical problems. The last observation carried forward (LOCF) approach was used to fill the missing data points. For the ingestion phase, gastric relaxation as well as stomach, meal and intragastric air volume was analysed using a paired-samples t-test. For the emptying phase, a two-factor (body position and time) repeated measures ANOVA with Greenhouse-Geisser correction was used to evaluate the effect of body position and time on total, proximal and distal meal volume as well as stomach and intragastric air volume. Analysing the interaction between body position and time allowed assessing differences in the characteristics of volume curves over time between RP and SP. In addition, meal volume at time  $t = 90$  min was compared using a paired-samples t-test. Gastric activity and mean peristaltic velocity was also analysed using a paired-samples t-test. Data are expressed and presented as median (interquartile range). A  $P$  value less than 0.05 was considered statistically

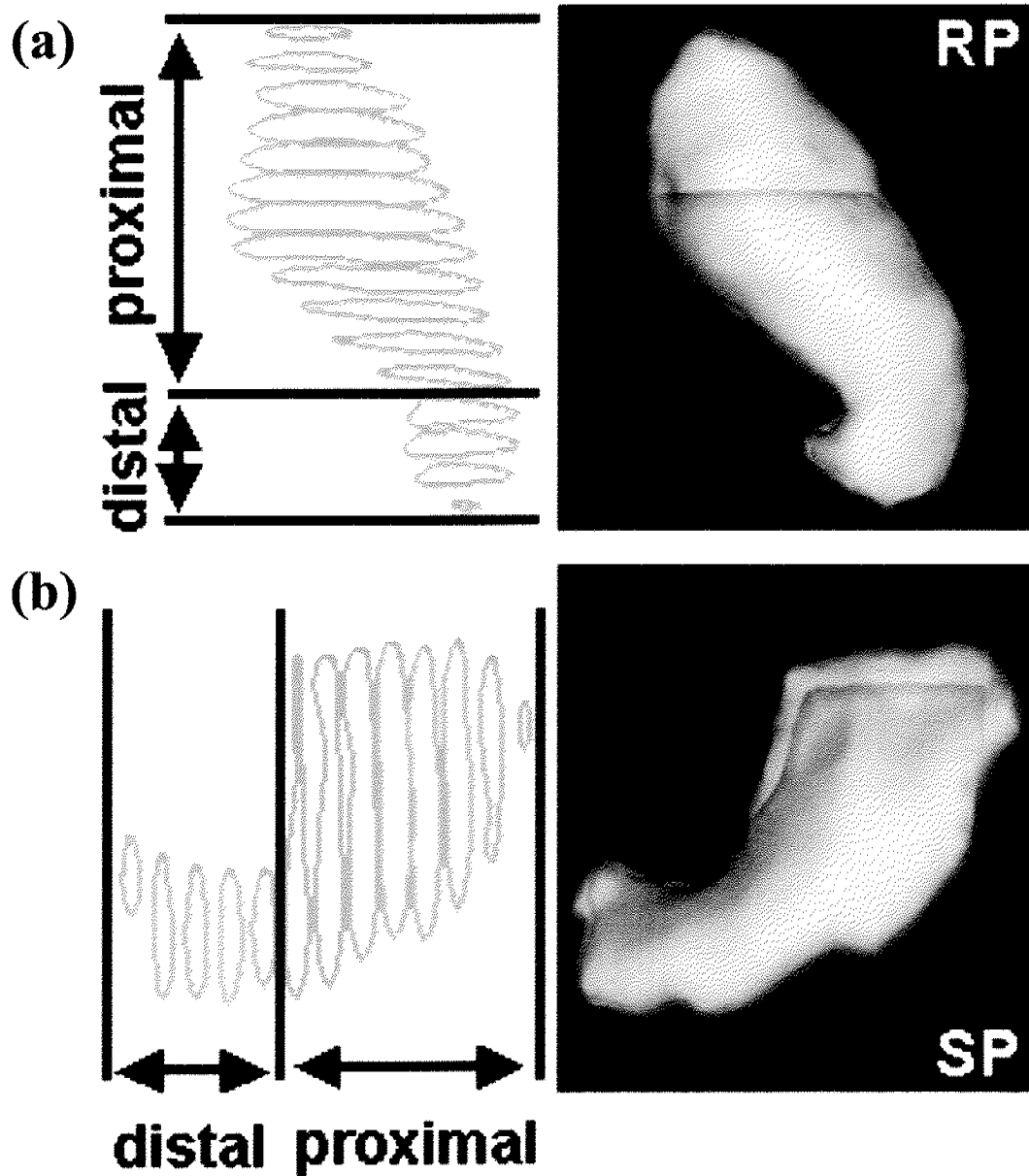
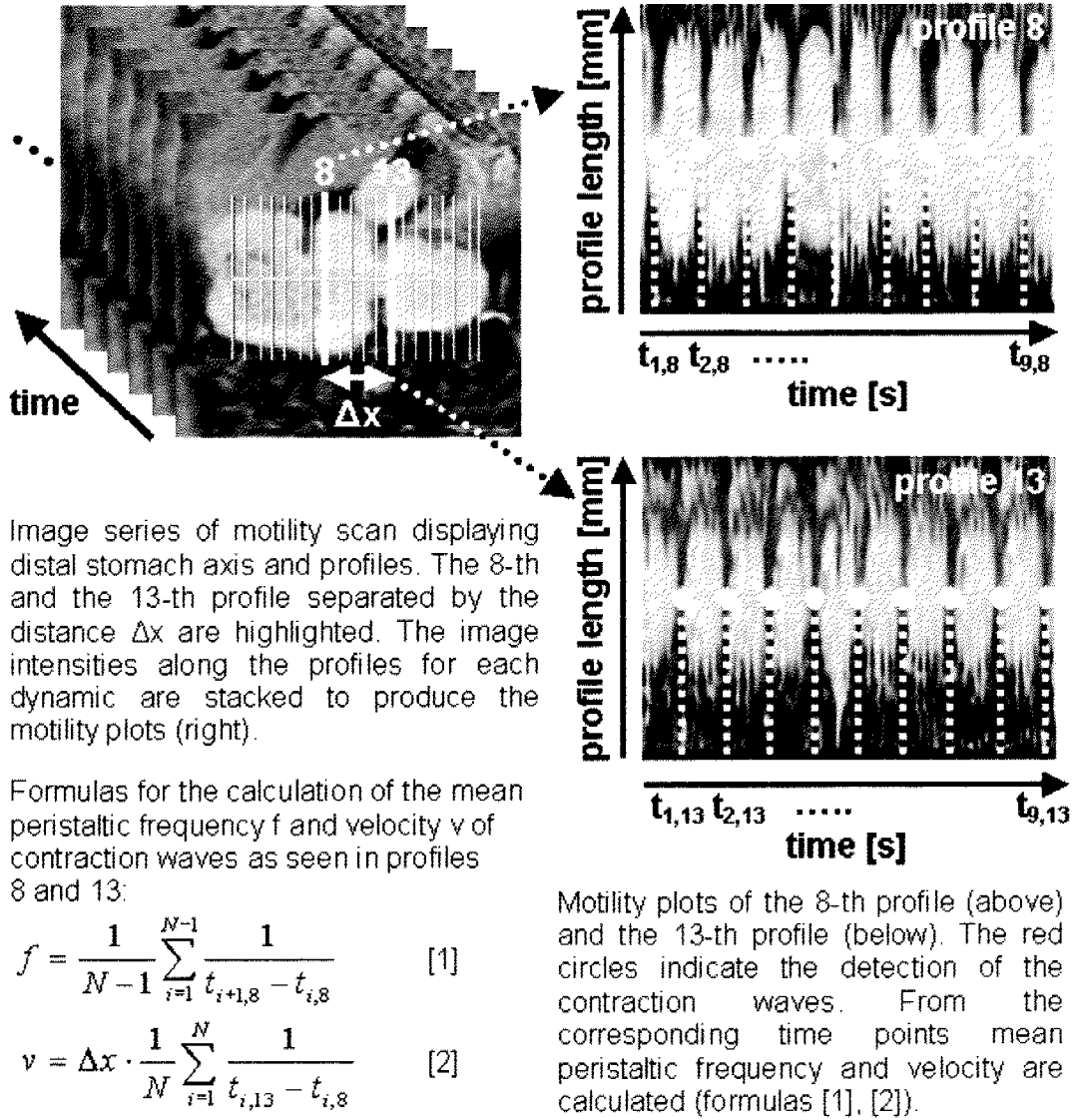


Figure 3.7: Three-dimensional stomach contours (left) and corresponding volume rendering of stomach and meal volume (right) 5 min after meal intake for RP (a) and SP (b). The separation into proximal and distal stomach is indicated in the contour plots by arrows (left). Stomach wall is rendered in transparent white and meal in solid red.



$N$ : number of detected contraction waves  
 $i$ : contraction wave index

Figure 3.8: MRI image processing for the analysis of gastric motility. Motility plots of profile 8 and 13 are used to illustrate the calculation of peristaltic frequency and velocity.

significant.

## Results

Image acquisition and analysis was successfully performed in all subjects. The image quality attained with both the whole-body and the open-configuration MRI system allowed semi-automated detection and computation of stomach, meal and intragastric air volume as well as peristaltic frequency and velocity. Three-dimensional visualisation of stomach together with gastric contents was performed to qualitatively assess intragastric meal distribution (figure 3.7a, b right).

### Ingestion phase

Stomach volume and intragastric air volume was not different between RP and SP for fasted condition, after solid meal intake and after liquid meal intake (3.2). Gastric relaxation showed no difference between RP and SP after solid as well as after liquid meal ingestion (3.2).

### Emptying phase

Stomach volume, meal volume and intragastric air volume (expressed in ml) over time is presented in figure 3.9. Gastric emptying curves (defined as normalised remaining meal volume over time and expressed as percentage) are presented in figure 3.10. Proximal and distal meal volume (expressed in ml) over time is presented in figure 3.11.

### Stomach volume

Stomach volume in RP was highest at time  $t = 5$  min and thereafter continuously decreased over time (figure 3.9). In SP stomach volume reached a maximum after complete meal ingestion at  $t = 0$  min. However, not until time  $t = 10$  min a continuous decrease was observed (figure 3.9). Statistical analysis showed a significant effect of time ( $P < 0.001$ ), a nonsignificant effect of body position and a nonsignificant interaction between body position and time.

### Meal volume

Gastric emptying curves showed different emptying dynamics for RP and SP, especially during the early post-prandial phase (figure 3.10). Statistical analysis showed a significant effect of time ( $P < 0.001$ ), a nonsignificant effect of body position and a significant interaction between body position and time ( $P < 0.05$ ) over total post-prandial period. For the early post-prandial period, statistical analysis showed a significant effect of time ( $P < 0.001$ ), a nonsignificant effect of body position and a significant interaction between body position and time ( $P < 0.05$ ). For the late post-prandial period, statistical analysis showed a significant effect of time ( $P < 0.001$ ), a trend for an effect of body position ( $P = 0.06$ ) and a significant interaction between body position and time ( $P < 0.05$ ). Remaining meal volume at  $t = 90$  min was smaller for RP compared to SP (RP: 229 ml (194–240 ml) vs. SP: 252 ml (206–290 ml),  $P < 0.05$ ).



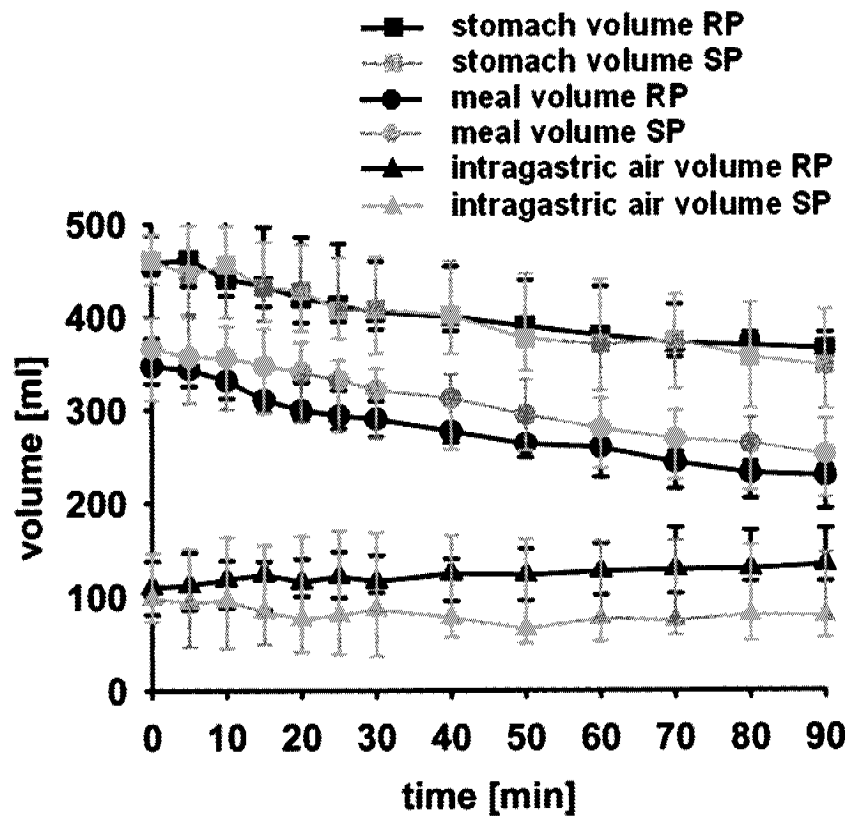


Figure 3.9: Stomach volume (■), meal volume (●) and intragastric air volume (▲) over post-prandial study period for RP (black) and SP (grey). The large interquartile ranges reflect the high inter-individual variability commonly observed for gastric emptying (and not measurement errors).

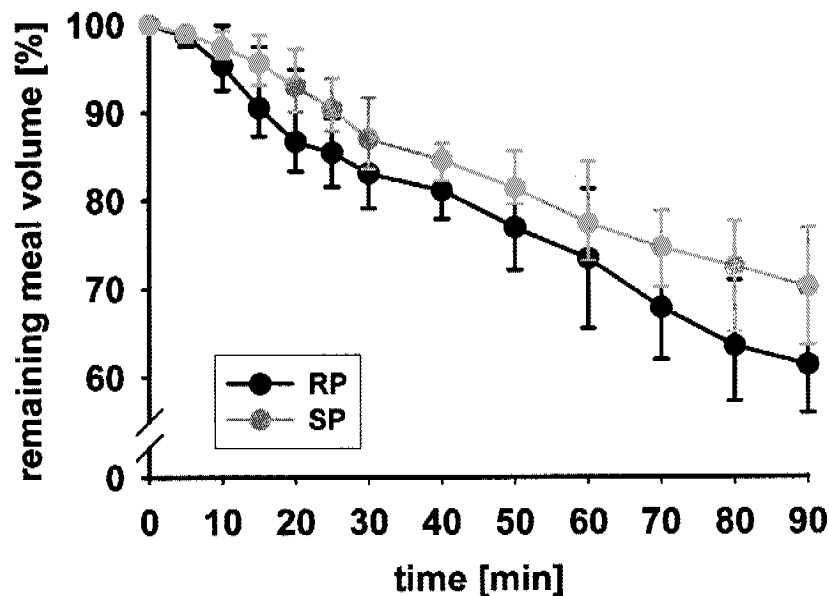


Figure 3.10: Normalised gastric emptying curves (percentage of remaining meal volume in the stomach) for RP (black) and SP (grey). A divergence of the emptying curves is observed, especially during the first 30 min after meal ingestion.

### Intragastric air volume

Initial intragastric air volume at time  $t = 0$  min was similar for RP and SP. Subsequently, intragastric air volume curves diverged over time (figure 3.9). Statistical analysis showed a nonsignificant effect of time, a significant effect of body position ( $P < 0.05$ ) and a trend for an interaction between body position and time ( $P = 0.06$ ) over total post-prandial period. For the early post-prandial period, statistical analysis showed a nonsignificant effect of time, a trend for an effect of body position ( $P = 0.07$ ) and a significant interaction between body position and time ( $P < 0.05$ ). For the late post-prandial period, statistical analysis showed a nonsignificant effect of time, a significant effect of body position ( $P < 0.05$ ) and a nonsignificant interaction between body position and time.

### Intragastric meal distribution

Proximal meal volume curves reflected the characteristics of total meal volume curves for both positions (figure 3.11). For proximal meal volume, statistical analysis showed a significant effect of time ( $P < 0.001$ ), a significant effect of body position ( $P < 0.05$ ) and a significant interaction between body position and time ( $P < 0.05$ ). For distal meal volume, statistical analysis showed a significant effect of time ( $P < 0.001$ ), a nonsignificant effect of body position and a nonsignificant interaction between body position and time. Statistical analysis of intragastric distribution showed a trend for an effect of time ( $P = 0.06$ ), a significant effect of body position ( $P < 0.05$ ) and a significant interaction between body position and time ( $P < 0.05$ ).

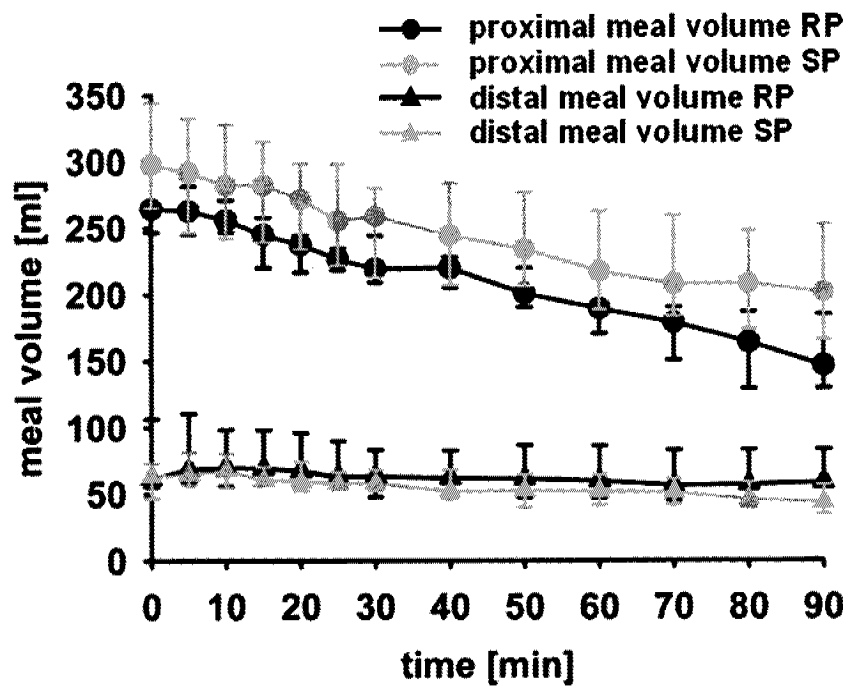


Figure 3.11: Proximal (●) and distal (▲) meal volumes over post-prandial study period for RP (black) and SP (grey). Proximal meal volume was different for the two body positions and showed different dynamics for the total emptying phase. Distal meal volume was similar for RP and SP and remained approximately constant over time.

	RP		SP	
	fasted	after solid	after liquid	fasted
SV (ml)	92 (76–142)	312 (289–353)	458 (446–488)	82 (75–125)
AV (ml)	69 (53–86)	97 (52–149)	110 (81–131)	67 (51–107)
GR (ml)		225 (184–244)	163 (118–176)	230 (184–254)
				153 (126–182)

Table 3.2: Stomach volume (SV), intragastric air volume (AV) and gastric relaxation (GR) during ingestion phase for RP and SP. No differences were found between the two body positions.

### Gastric peristalsis

Gastric activity was not different for RP and SP (RP:  $3.1 \text{ min}^{-1}$  ( $3.0\text{--}3.2 \text{ min}^{-1}$ ) vs. SP:  $3.1 \text{ min}^{-1}$  ( $2.9\text{--}3.3 \text{ min}^{-1}$ ), n.s.). There was a small difference in peristaltic velocity for the two body positions (RP:  $2.6 \text{ mm/s}$  ( $2.3\text{--}3.3 \text{ mm/s}$ ) vs. SP:  $2.4 \text{ mm/s}$  ( $2.2\text{--}3.0 \text{ mm/s}$ ),  $P < 0.05$ ). For both positions, no correlation was found between peristaltic velocity and gastric emptying.

### Discussion

This study demonstrated the effect of body position on gastric motor function as assessed by MRI. It is the first time, a study simultaneously analysed the posture dependency of 8 relevant gastric parameters. Stomach, meal and intragastric air volume, gastric relaxation, gastric emptying, intragastric meal distribution and peristaltic frequency and velocity were successfully assessed in right decubitus (RP) as well as in seated (SP) body position using different MRI systems. Results highlight that gastric MRI in the right decubitus body position represents a valuable and non-invasive imaging technique for the assessment of human gastric function.

RP was chosen for imaging in the whole-body MRI system because this body position provided the most similar stomach configuration compared to SP, i.e. the distal stomach was always filled with gastric contents and intragastric air was confined to the proximal stomach (figure 3.7a). Gastric volume responses for the ingestion phase were not different and stomach volume remained similar throughout the complete study period for the two body positions. An effect of body position was found for post-prandial intragastric air volume. This effect was explained by significant different dynamics in the meal emptying between RP and SP. This different emptying dynamics produced a trend for an effect of body position on late post-prandial meal volume and finally resulted in a slightly larger meal volume for SP at time  $t = 90 \text{ min}$  (RP:  $229 \text{ ml}$  vs. SP:  $252 \text{ ml}$ ).

A significant however clinically not relevant difference in gastric emptying was detected. The difference in emptying dynamics and meal volume after 90 min between RP and SP was subtle and small compared to the changes observed for meal emptying in patients diagnosed with gastroparesis.<sup>150</sup> Since gastric activity (mean peristaltic frequency) was similar for both positions and also the slightly faster peristaltic velocity for RP did not explain the accelerated emptying, gastric peristalsis was excluded as cause for the found difference in meal emptying. This is in agreement with results of recent studies using MRI<sup>4</sup> and duplex sonography<sup>5</sup> both combined with intraluminal manometry. These studies showed that rather a gastroduodenal pressure difference than gastric peristalsis appears to be the major driving force for meal emptying. Such pressure difference between stomach and duodenum is determined by the intragastric pressure (IGP). IGP itself is influenced by the intra-abdominal pressure (IAP) and the gastric wall tension. In this non-invasive study, no in vivo pressure or strain measurements were performed to detect these parameters. However, differences in IGP, IAP and gastric tone between the two body positions can be assumed indirectly from gastric volumes. In respiratory medicine as well as for the gastric barostat technique IAP is approximated from fasted IGP.<sup>151,152</sup> Based on the thermodynamic interrelation between air pressure and air volume ( $p \cdot V = \text{const}$ ), comparison of fasted intragastric air volume allows an indirect determination of

possible differences in IAP between RP and SP. Since fasted intragastric air and stomach volume was not different for both positions, IAP was assumed to be similar for RP and SP during the complete study period. This assumption implies that initial post-prandial IGP must have been higher in RP since emptying curves (figure 3.10) diverged from the beginning of the emptying phase (and stomach volume remained similar). Similar initial meal and stomach volumes indicated that increased IGP was generated by higher intragastric air pressure. MRI volume data of RP and corresponding three-dimensional visualisation (figure 2a) showed that gastric contents were located above the LES preventing intragastric air to be belched. Thus, swallowed air during liquid ingestion was trapped inside the proximal stomach in RP and could have increased IGP. This is indirectly supported by the higher inter-individual variability in intragastric air volume for SP where air could be expelled from the stomach (figure 3.9). Obviously, a higher IGP in RP could only be maintained by concurrently increased gastric wall tension (gastric tone). An increased vagal stimulation in the lying position,<sup>144,153,154</sup> especially in RP<sup>155,156</sup> might have induced such higher gastric tone.

In case IGP and gastric tone (and gastric peristalsis) may be independent of posture, gastric outflow resistance as major control mechanism of gastric emptying<sup>5,28,157</sup> (16, 24, 25) would present the only remaining parameter causing the different emptying dynamics. Animal studies showed that pyloric function is also modulated by vagal activity. It was shown that vagal stimulation reduces pyloric resistance and increases transpyloric stroke volume,<sup>158,159</sup> whereas vagal blockade provokes the opposite.<sup>160,161</sup> This effect of vagal stimulation on gastric tone (increase) and pyloric resistance (reduction) indicates that vagal stimulation might present the physiological cause for the accelerated meal emptying in RP.

The current study demonstrates that MRI is a sensitive, non-invasive imaging technique for the measurement of gastric volume and motor function. Despite large inter-individual variations (figure 3.9), small differences in gastric emptying were detected. Such high sensitivity to subtle differences in the emptying characteristics is currently not attainable with  $\gamma$ -scintigraphy and SPECT. Although these techniques are considered the gold standard for gastrointestinal imaging they have many disadvantages compared to MRI. Scintigraphy is restricted to two-dimensional imaging of poor image resolution and needs corrections for background noise and decay. Spatial and temporal resolution of dynamic scintigraphy is very low compared to dynamic MRI (scintigraphy:  $5 \times 5 \text{ mm}^2$  at 20 frames per minute vs. MRI:  $1.4 \times 1.4 \text{ mm}^2$  at 140 frames per minute).<sup>162</sup> Using SPECT, the duration for gastric volume acquisition ranges from 3–7 min at an image resolution of  $3 \times 3 \text{ mm}^2$ .<sup>163–165</sup> In the current study using MRI, complete volume acquisition was achieved within 15–44 s at an image resolution of  $1.4 \times 1.4 \text{ mm}^2$ . Furthermore, neither separation of gastric contents and intragastric air nor simultaneous assessment of gastric volume and peristalsis is feasible using the nuclear imaging techniques.

In conclusion, gastric MRI performed in the right decubitus lying body position is feasible for GI clinical research on gastric motor function and diagnosis of gastroparesis and gastric motility disorders. The physiological discussion on IGP, gastric tone and pyloric resistance indicated that posture dependent vagal activity induced the different emptying characteristics observed for RP and SP. MRI as highly sensitive and non-invasive imaging technique has the potential to become the method of choice for the assessment of GI function in humans.

## **Acknowledgment**

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### 3.3 The effect of macronutrient on gastric volume response, emptying and dyspeptic symptoms - a Magnetic Resonance Imaging study

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## Abstract

*Aim:* To study the effects of three different liquid macronutrient on gastric volume changes, emptying and on gastrointestinal symptoms as well as the effect of posture in healthy volunteers using magnetic resonance imaging (MRI).

*Methods:* In randomised order, three different liquid meals of 500 ml (fat emulsion, 375 kcal; protein solution, 375 kcal; glucose solution, 400 kcal) were infused via a nasogastric tube into the stomach of twelve healthy volunteers on four different occasions. Three studies were performed in seated (SP) and one study in right decubitus body position (RP). MRI sequences covering the complete gastric region were performed prior to and at  $t=0,3,6,12,15,25, 35,45,60,75,90$  min after meal administration. Stomach, meal and intragastric air volumes were measured. AUC's for early and late emptying phases were calculated and amplitude and dynamics of the volume curves were analysed by a linear exponential model. Gastrointestinal symptoms were assessed by a self-report scale.

*Results:* In both positions, initial (0–45 min) postprandial gastric volumes were highest for glucose ( $p < 0.05$ ). Initial emptying was higher for fat and protein ( $p < 0.05$ ). The initial amplitude and dynamics of the volume curves for stomach and meal were uniform for all macronutrient and positions. Meal emptying was not affected by body position, however, in RP stomach volumes were higher than in SP during the late emptying phase ( $p < 0.01$ ). Perception of fullness and satiety were associated with postprandial gastric volumes ( $r=0.94$ ,  $p < 0.001$ ), but not with macronutrient composition. *Conclusion:* Isovolumic/isocaloric liquid macronutrient meals modulate gastric volume response by different initial meal emptying patterns and secretion. Volume responses, emptying and perception was independent of posture. Under physiological conditions macronutrient specific accommodation responses, as shown in barostat studies, are not reflected as gastric volume responses.

## Introduction

The volume response of the stomach to meal ingestion, commonly referred to as gastric accommodation, consists of a relaxation of the proximal and distal stomach<sup>163</sup> enabling the accommodation of the meal volume load without a rise in pressure.<sup>166</sup> Generally, the accommodation reflex is subdivided into two components: first, reflex or receptive relaxation almost instantaneously providing the required reservoir volume for the ingested meal and second, an adaptive relaxation, which occurs after the initial gastric volume increase with further modulation of gastric tone, possibly by specific nutrients,<sup>60</sup> and might contribute to the regulation of gastric emptying. Although the accommodation response has been extensively studied in animals and humans, the factors controlling food-induced relaxation are still incompletely understood. Questions such as the relationship of the magnitude of the response to different caloric densities, or to different composition of isocaloric meals are still unanswered.<sup>167</sup>

Despite extensive basic research, the common clinical problem of functional dyspepsia and the interest in the possible role of reduced post-prandial accommodation in the pathogenesis of dyspeptic symptoms, there are considerable difficulties in measuring the accommodation process.<sup>54,168</sup> Hence, advantages, disadvantages and potential clinical applications of invasive techniques (gastric barostat), volumetric imaging techniques (three-dimensional ultrasound, single photon emission tomography, magnetic resonance imaging) and non-

imaging assessments (satiety drinking, waterload test) for the measurement of gastric accommodation are still under discussion.<sup>57,163,169,170</sup>

Since gastric accommodation cannot be seen in isolation from gastric active (tone) and passive tissue properties, gastric motility and gastric emptying, the interaction between these motor events in the process of storage and emptying of a meal should be ideally assessed simultaneously with a single technique. Magnetic resonance imaging (MRI) allows measurement of gastric motility and emptying with high spatial and temporal resolution and has recently been proposed as a technique for the measurement of postprandial volumes of different regions of the stomach, with the objective of being able to assess postprandial gastric accommodation.<sup>60,171,172</sup> This technique has been validated for measurement of gastric contractile activity and gastric emptying.<sup>14,16</sup> Additionally, the use of an open configuration MRI system allows the investigation of subjects in the seated body position and thus account for differences in gastric physiology due to gravitational effects.<sup>40,173</sup>

The aim of this study was to measure simultaneously the gastric volume responses after the ingestion of meals of different macronutrient content, the related gastric emptying and gastrointestinal perception in healthy volunteers. We hypothesised that changes in gastric tone for isovolumic and isocaloric liquid meals of different macronutrient content, as shown in recent invasive studies using the gastric barostat technique, induce comparable gastric volume responses under non-invasive conditions. The barostat technique detected different effects on gastric relaxation and on sensory responses following duodenal infusion of fat, protein or mixed nutrients during sustained gastric distension (mimicking the intragastric presence of food) were demonstrated.<sup>174</sup>

Since the intragastric distribution of a liquid meal affects gastric motor activity and gastric emptying,<sup>18,42,137</sup> data on gastric volume responses and emptying were mainly obtained in the upright seated, i.e. the physiological position. To analyse the effect of posture on gastric volume responses and emptying, additional measurements were performed in the right decubitus body position.

## Methods

This prospective study was approved by the local Institutional Review Board and informed consent was obtained from all volunteers.

### Subjects and Study Design

Twelve healthy subjects [five men; age: 19–42 years (mean 31 years); body mass index:  $22.2 \pm 0.7$  kg/m<sup>2</sup>] participated in the study. No volunteer had a history of digestive system disease, and none were taking medication that might affect gastric motility or sensation. Subjects were studied after an overnight fast on 4 different morning sessions, separated by at least 1 week. At each session they received one of three isovolumic (500ml) and isocaloric (375–400 kcal) liquid meals of different macronutrient content in randomised order. According to a fractional study design, subjects were examined in seated body position (SP) during three sessions and in the right decubitus body position (RP) in one additional session.

### Test Meals

The three test meals were: (A)  $68.2 \text{ g} \cdot \text{l}^{-1}$  soy bean oil emulsion (Intralipid<sup>®</sup>, Fresenius Kabi AG, Stans, Switzerland), 375 kcal, 308 mosm/l (referred to as fat), (B)  $200 \text{ g} \cdot \text{l}^{-1}$  glucose solution, 400 kcal, 1110 mosm/l (referred to as glucose) or (C)  $200 \text{ g} \cdot \text{l}^{-1}$  albumin solution (Albumin ZLB 20% <sup>®</sup>, ZLB AG, Bern, Switzerland), 375 kcal, 308 mosm/l (referred to as protein). Fat solution was derived by diluting original Intralipid<sup>®</sup> 10% solution with water and  $3.82 \text{ g} \cdot \text{l}^{-1}$  NaCl. The emulsion comprised 52% linoleic acid, 22% oleic acid, 13% palmitic acid, 8% linolenic acid, 4% stearic acid, 1% other fatty acids and  $8.184 \text{ g} \cdot \text{l}^{-1}$  egg phospholipids and  $15 \text{ g} \cdot \text{l}^{-1}$  glycerin. To test acid stability, five 250 ml samples of lipid 6.82% solution were mixed with 1 n hydrochloric acid until a final pH of 1.5 was reached, and then incubated for 8 h at 37°C. During this period, no break down in two phases and no fat layering was observed. All meals were labeled with 500  $\mu\text{M}$  Gd-DOTA (gadolinium tetra-azacyclododecane tetra-acetic acid; Dotarem<sup>®</sup>; Laboratoire Guerbet, Aulnay-sous-Bois, France) to enhance image contrast between the stomach content and the surrounding tissue.

### Magnetic Resonance Imaging

Measurements in SP were performed using the 0.5 T open-configuration MRI system (Signa SP/i 0.5 T, GE Medical Systems, Milwaukee, WI, USA) and in RP using the 1.5 T whole-body MRI system (1.5 T Intera, Philips Medical Systems, Best, The Netherlands). After localisation of the stomach and imaging the preprandial stomach volume and gastric content volume at  $t = -5 \text{ min}$  ( $V_{\text{fasting}}$ ), the test meal infusion was performed with the volunteer positioned in SP or RP in the respective MRI system. The 500 ml meal was continuously infused over 5 min at 100 ml/min by a nasogastric tube (Ch 12) using a perfusion pump. Subsequently, starting at  $t = 0 \text{ min}$ , MRI volume scans imaging the post-prandial stomach and meal volumes were performed every three 3 minutes until  $t = 15 \text{ minutes}$ , then every 10 minutes until  $t = 45 \text{ minutes}$  and every 15 minutes until  $t = 90 \text{ minutes}$  after gastric infusion. On the 0.5 T MRI system, a fast spoiled gradient echo (FSPGR) sequence was used for imaging. Imaging parameters of the volume scan for this system were: 20 sagittal image planes (covering the total gastric region); repetition time, 170 ms; echo time, 7.5 ms; flip angle, 60°; field of view, 350 mm; slice thickness, 10 mm; interslice gap, 0 mm; matrix, 256×192 pixels; two breath holds of 22 seconds. A standard abdominal send/receive coil was used for excitation and acquisition. On the 1.5 T MRI system, a gradient refocused steady state free precession (SSFP) sequence was used for imaging. Imaging parameters for this system were: 20 sagittal image planes; repetition time, 3.5 ms; echo time, 1.7 ms; flip angle, 60°; field of view, 380 mm; slice thickness, 10 mm; interslice gap, 0 mm; matrix, 256×205 pixels; one breath hold of 11.5 seconds). The quadrature body-coil was used for excitation and acquisition.

### Image Analysis

Total gastric area was outlined in each image of a MRI volume scan. Based on this segmentation, stomach and meal volume was determined over time. Stomach volume was calculated by summing the outlined pixels in each image slice and integrating the sum over all slices. Due to the distinct positive signal intensity of the meal compared to intragastric air, meal volume was identified by applying a manually selected intensity threshold. Sum-

ming the identified pixels with intensity larger than the selected intensity threshold and integrating the sum over all slices resulted in the meal volume. The difference between computed stomach and meal volume resulted in the intragastric air volume.

### Symptom Questionnaire

A self-report scale was used to assess volunteer's perception of gastrointestinal symptoms before and after meal administration.<sup>37</sup> The volunteers were instructed to give a number between 0 and 10 (0 = no symptoms; 10 = maximum symptoms) to indicate their perception of fullness, satiety, nausea and bloating preprandial and at times  $t = 0, 3, 6, 15, 25, 35, 45, 60, 75, 90$  min.

## Data analysis

### Analysis of gastric meal volume curves

The study period was sub-divided into three phases, the infusion phase ( $t_{-5}-t_0$ ), the early emptying phase ( $t_0-t_{45}$ ) and the late emptying phase ( $t_{45}-t_{90}$ ). Gastric relaxation ( $V_{relaxation}$ ) was defined as the volume difference between the initial stomach volume at  $t = 0$  min post infusion ( $V_0$ ) and the fasting stomach volume at  $t = -5$  min ( $V_{fasting}$ ). Stomach, meal and intragastric air volumes were plotted over time to generate volume curves (figure 3.12). The area under the volume curves (AUC [l·min]) for the time intervals  $\Delta t = 0-15$  min ( $AUC_{0-15}$ ),  $0-45$  min ( $AUC_{0-45}$ ),  $45-90$  min ( $AUC_{45-90}$ ) and  $60-90$  min ( $AUC_{60-90}$ ) were calculated using the trapezoid method.

To analyse the characteristics of the volume curves, the data were fitted to a three-parameter linear exponential gastric emptying model (LinExp). The model formula is given as  $V(t) = V_0(1 + \kappa t/t_{empt}) \exp(-t/t_{empt})$ , where  $V_0$  is an estimate of the volume post infusion at  $t_0$  [ml] and  $t_{empt}$  is the emptying time constant [min]. The dimensionless positive parameter  $\kappa$  (kappa) models the initial lag phase; for  $\kappa=0$ , the formula reduces to exponential emptying. This model was recently introduced<sup>61,175</sup> to complement the power exponential gastric emptying model (PE model) for normalised volume data described by *Elashoff et al.*<sup>176</sup> The advantage of the LinExp model is that it can emulate an initial increase of the volume curve, whereas the PE model is limited to monotonically decreasing emptying curves.

### Gastrointestinal symptom scores

The gastrointestinal symptom scores were plotted against time. AUC over 90 minutes of the self report scores were used to compare the effects of the different macronutrient on symptoms. The averaged symptom scores at each time point were plotted against total stomach and meal volumes. Linear regression analysis was used to assess the relationship between symptom scores and gastric content.

### Statistical Analysis

Statistical descriptive calculations, calculations for linear regression analysis and (Spearman) correlation analysis were performed using the data analysis and graphics package R.<sup>177</sup> To stabilise parameters estimates ( $V_0$ ,  $\kappa$ ,  $t_{empt}$ ) of the LinExp model, these were

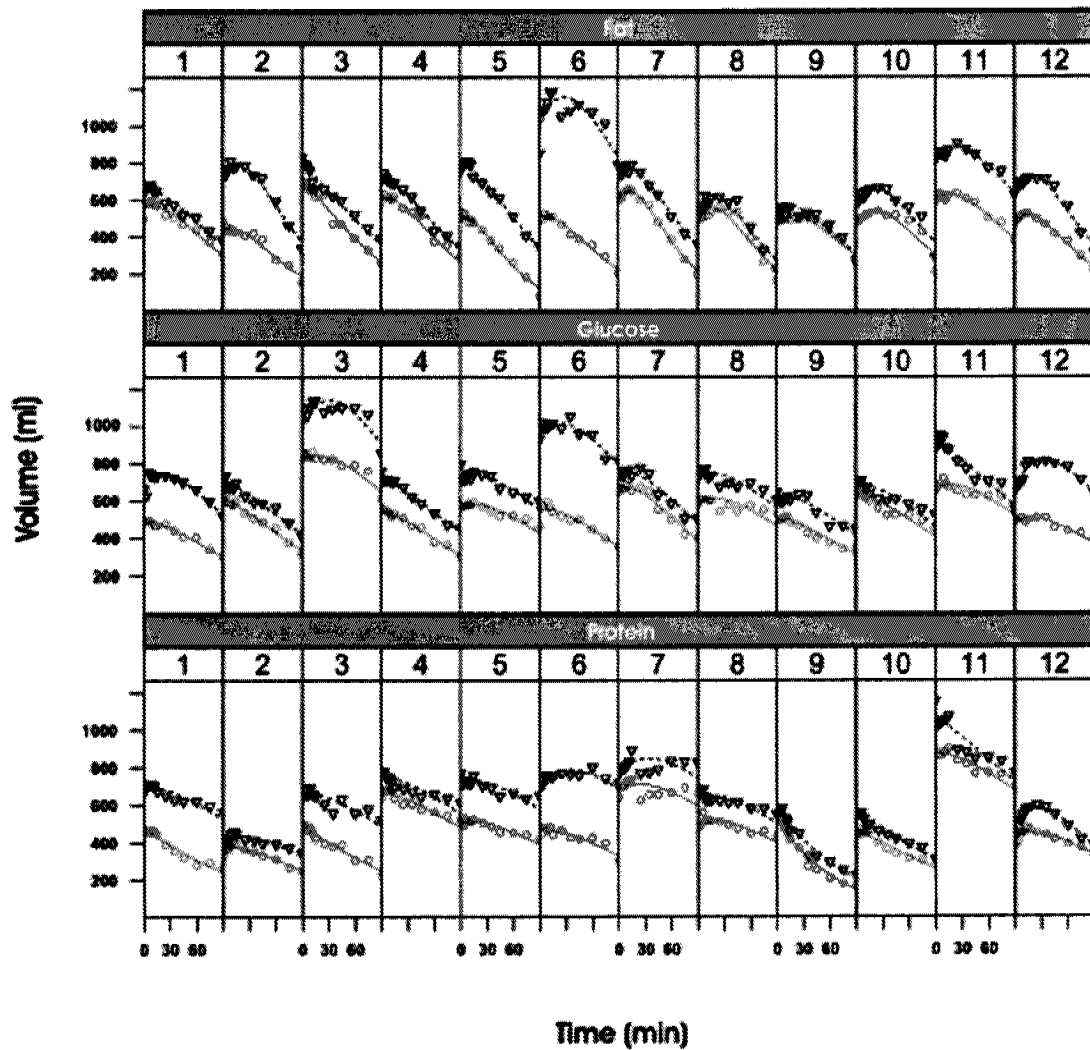


Figure 3.12: Volume curves for stomach ( $\nabla$ ) and meal ( $\circ$ ) volumes of 12 subjects and three isocaloric (375–400 kcal) and isovolumic (500 ml) liquid meals of different macronutrient content in seated position. Lines were computed from the coefficients estimated in the overall fit to linear exponential model (dashed lines: stomach volumes; solid lines: meal volumes).

not determined from individual curve fits, but estimated from a single statistical fit to all volume data using the **R** library *nlme*.<sup>178</sup> The half-emptying time ( $t_{50}$ ) for stomach and meal volume was determined from the parameters  $\kappa$  and  $t_{empt}$  by Newton approximation. Average volume curves for each meal and position were calculated. The slopes of individual intragastric air volume curves ( $Air_{slope}$ ) were determined by linear regression analysis. Effects of macronutrient were compared using a mixed model ANOVA, with 'subject' as a random variable and 'treatment' and 'meal/stomach' as fixed variables. Effects of body position were compared for 'meal', 'stomach' and 'intragastric air' with 'subject' as a random variable and 'treatment' and 'position' as fixed variables for between- and within-group analysis.<sup>178</sup> Data were considered to be significant at  $\alpha < 0.05$ . In addition a Bonferroni correction was applied for three pairwise comparisons of each macronutrient. Data are presented as mean  $\pm$  SEM. The results presented in the tables are group mean averages calculated by ANOVA and differ slightly from the raw data presented in the figures.

## Results

Image acquisition and analysis were performed successfully in all subjects. The image quality attained with both the whole-body and the open configuration MRI system allowed semi-automated detection and computation of stomach, meal and intragastric air volumes.

### Gastric volume responses

#### *Infusion phase ( $t_{-5}-t_0$ )*

$V_{fasting}$  for stomach volume and gastric content between treatment groups and body positions was not different (tables 3.3, 3.4). After infusion,  $V_0$  for meal and stomach was higher for glucose than for protein and fat in SP ( $p < 0.01$ ).  $V_{relaxation}$  was highest for glucose in both body positions with differences between glucose and protein or fat in SP ( $p < 0.01$ ; table 3.3). In RP,  $V_{relaxation}$  was larger for glucose than protein ( $p < 0.05$ ; table 3.4). In SP, initial meal emptying was higher for fat and protein than for glucose (fat,  $-37 \pm 17$  ml; protein,  $-42 \pm 22$  ml vs. glucose:  $17 \pm 22$  ml,  $p < 0.05$ ). Postprandial intragastric air increased significantly in both positions (mean air increase: SP,  $57 \pm 15$  ml and RP,  $25 \pm 7$  ml;  $p < 0.01$ ) with a similar volume for each macronutrient. In SP,  $V_{relaxation}$  for the stomach was associated with intragastric air increase ( $r = 0.67$ ,  $p < 0.001$ ).

	Fat		Glucose		Protein	
	Meal	Stomach	Meal	Stomach	Meal	Stomach
$V_{fasting}$ [ml]	65±22	178±18	67±22	180±18	62±23	175±18
$V_0$ [ml]	532±27	696±22	596±27 <sup>++</sup>	759±22 <sup>++</sup>	520±32	683±22
$V_{relaxation}$ [ml]	460±17	517±14	525±17 <sup>++</sup>	581±14 <sup>++</sup>	451±17	508±14
$\kappa$	1.34±0.1*	1.41±0.08*	1.14±0.1	1.21±0.08	1.05±0.1	1.12±0.08
$t_{50}$ [min]	87±8 <sup>***</sup>	104±7 <sup>***</sup>	126±8	143±7	130±7	147±7
$AUC_{0-15}$ [l·min]	8.4±0.4	10.9±0.4	9.1±0.4†	11.6±0.4†	7.8±0.5	10.4±0.4
$AUC_{0-45}$ [l·min]	23.9±1.3	31.8±1.1	26.1±1.3†	33.0±1.1†	21.8±1.5	29.7±1.1
$AUC_{60-90}$ [l·min]	9.6±1.1**	14.7±0.9**	14.0±1.1	19.0±0.9	12.1±1.2	17.2±0.9

<sup>++</sup>  $p < 0.01$  vs. protein, fat

†  $p < 0.01$  vs. protein

\*  $p < 0.05$  vs. protein, glucose

\*\*  $p < 0.01$  vs. protein, glucose

\*\*\*  $p < 0.001$  vs. protein, glucose

denote: for all parameters, except for  $\kappa$ ,  $p < 0.01$  for meal vs. stomach

Table 3.3: Effects of three different macronutrient on gastric volume response in 12 healthy volunteers in seated body position.



	Fat		Glucose		Protein	
	Meal	Stomach	Meal	Stomach	Meal	Stomach
<b>Seated</b>						
$V_{fasting}$ [ml]	17±37	141±58	28±37	130±58	66±31	187±48
$V_0$ [ml]	523±48	679±74	586±48	730±74	527±39	619±58
$V_{relaxation}$ [ml]	510±27	558±41	551±27†	599±41 <sup>+</sup>	468±22	460±31
$\kappa$	1.12±0.28	1.18±0.3	1.10±0.28	1.21±0.36	0.76±0.21	0.88±0.27
$t_{50}$ [min]	102±29	149±29	158±29	204±28*	123±21	152±21*
<b>Right decubitus</b>						
$V_{fasting}$ [ml]	52±31	180±47	63±31	169±47	101±31	226±47
$V_0$ [ml]	540±39	731±51	586±39	782±51	544±39	671±51
$V_{relaxation}$ [ml]	483±20	562±23	512±20†	603±23 <sup>+</sup>	432±20	464±23
$\kappa$	1.20±0.14	1.14±0.16	1.20±0.14	1.17±0.16	0.87±0.14	0.84±0.16
$t_{50}$ [min]	83±11	96±14*	139±11	152±14*	105±11	101±14*

†  $p < 0.05$  vs. protein<sup>+</sup>  $p < 0.01$  vs. protein\*  $p < 0.01$  vs. upright

Table 3.4: Effects of body position on gastric volume responses in 12 healthy volunteers. Each macronutrient was tested for both positions in 4 subjects.

	AUC <sub>0-90</sub> [l·min]		
	Fat	Glucose	Protein
Fullness	355±37	255±37	296±47
Satiety	431±45	336±45	369±61
Nausea	110±28**	35±28	40±30
Bloating	50±10	21±10	34±19

\*\*  $p < 0.01$  vs. protein, glucose

Table 3.5: Sensory responses in 12 healthy volunteers after infusion of three different macronutrient in the seated body position.

#### **Early gastric emptying phase ( $t_0-t_{45}$ )**

The stomach and meal volume curves of glucose and fat were characterised by a prominent initial volume increase followed by a continuous gastric emptying pattern. For protein, this initial volume increase was only small or not detectable (figure 3.12). AUC<sub>0-15</sub> and AUC<sub>0-45</sub> were higher for glucose than for protein in SP ( $p < 0.01$ ; figure 3.13, table 3.3) and RP ( $p < 0.05$ , data not shown). In SP, the initial increase in meal and stomach volume, indicated by the coefficient  $\kappa$ , was larger for fat than for glucose ( $p < 0.05$ ) and protein ( $p < 0.01$ ). For both positions and for all test meals, the initial volume increases were similar for meal and stomach volume. This is reflected by the similar  $\kappa$  values ( $p = 0.37$ ) given in tables 3.3 and 3.4. During this time interval intragastric air remained constant and was not different between the treatment groups ( $p > 0.05$ , data not shown).

#### **Late emptying phase ( $t_{45}-t_{90}$ )**

In SP, fat emptied faster than glucose or protein ( $p < 0.001$ ; table 3.3). In RP, a trend for a faster gastric emptying of the fat meal was observed ( $p = 0.09$ ; table 3.4). Meal emptying was not affected by body positions. In contrast,  $t_{50}$  of the stomach volume was longer for RP compared to SP ( $p < 0.01$ ; table 3.4) accompanied by a higher stomach volume in the late emptying phase (mean stomach AUC<sub>45-90</sub>: RP, 29.6 vs. SP, 24.7 l·min,  $p < 0.05$ ) and a linearly increasing intragastric air volume during this period (figure 3.13). This was supported by the computed values for Air<sub>slope</sub>, which were significantly different from zero only for RP and higher than in SP (mean Air<sub>slope</sub>: RP, 0.79 vs. SP, 0.02;  $p < 0.01$ ) and by higher AUC<sub>60-90</sub> for air volumes for all preparations (mean air AUC<sub>60-90</sub>: RP, 5.3 vs. SP, 3.8 l·min;  $p < 0.05$ ).

### **Sensory responses**

There were no differences in sensory responses for fullness, satiety and bloating between the test meals in both body positions. For SP, perception scores for nausea were higher for fat than for glucose or protein ( $p < 0.05$ ). For RP, nausea scores were not different (data for RP not shown, table 3.5). A linear relationship was found for meal or stomach volume and the perception of fullness and satiety for SP (figure 3.14) and RP (data not shown). A weak association was observed between the sense of nausea and total meal/stomach volume (nausea-scores for SP: lipid,  $R^2=0.50$ ; glucose,  $R^2=0.42$  and albumin,  $R^2=0.44$ ;  $p < 0.05$ ). No relationship was found for bloating (data not shown).

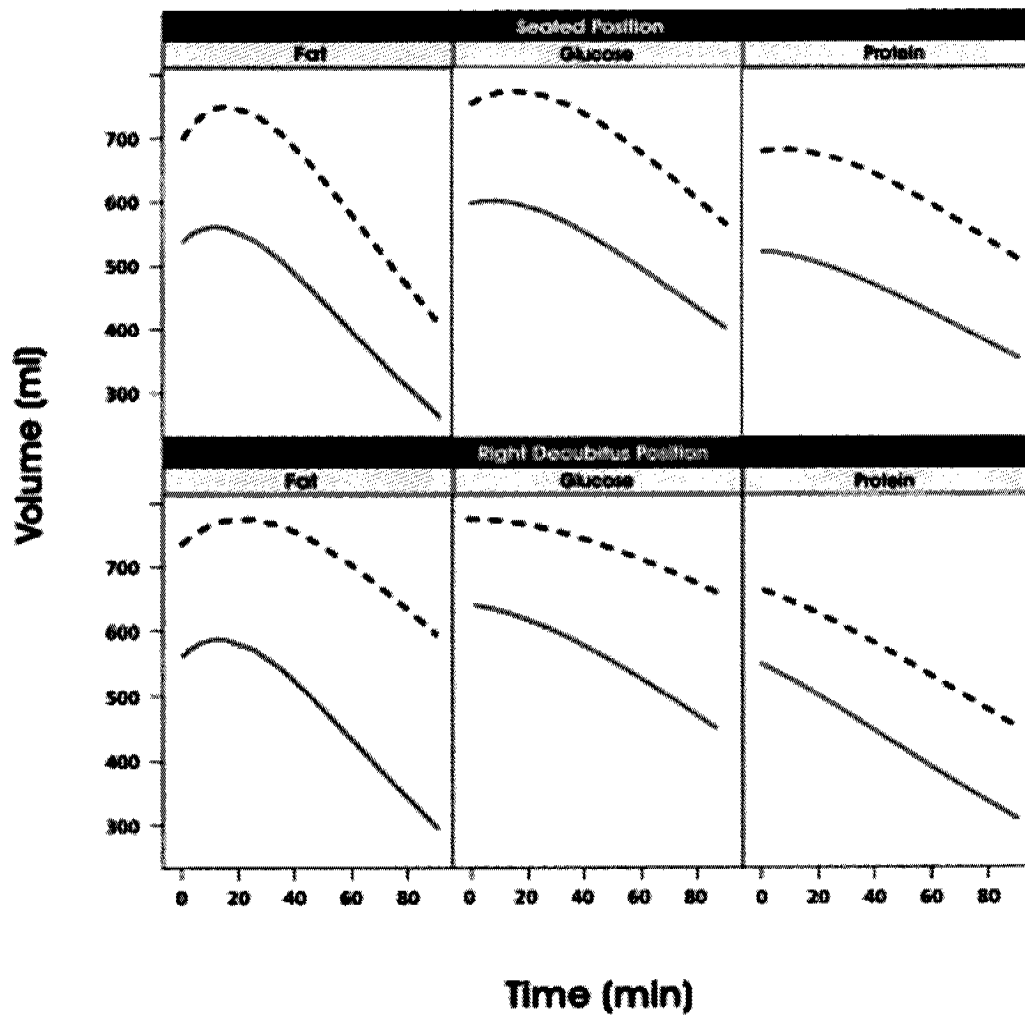


Figure 3.13: Average stomach (dashed lines) and meal volume curves (solid lines) of 12 subjects and three isocaloric (375–400 kcal) and isovolumic (500 ml) liquid meals of different macronutrient content in seated and lying position. Each macronutrient was tested for both positions in 4 subjects. Average stomach and meal volumes for both positions were computed from the averaged coefficients, estimated in the overall fit to the linear exponential model.

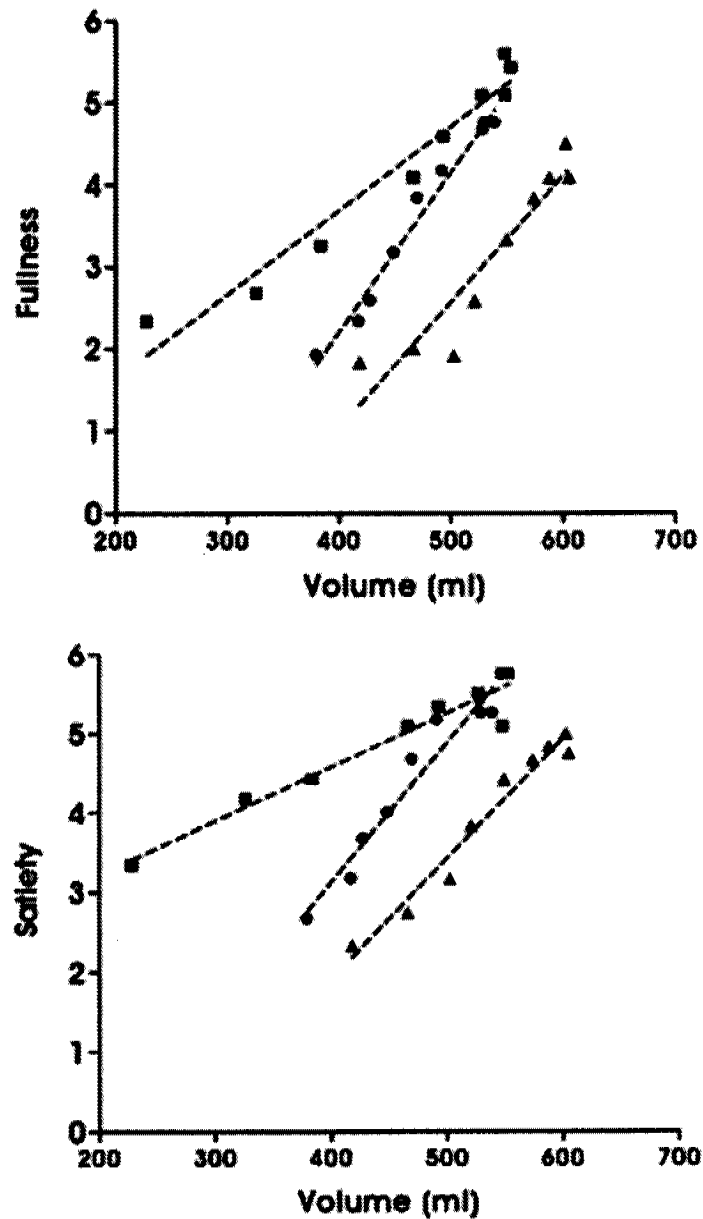


Figure 3.14: Association between mean meal volume and perception of fullness (A) and satiety (B) for the three different nutrient liquid meals in seated position (■: fat; ▲: glucose; ●: protein; A:  $R^2=0.98$  for fat,  $R^2=0.85$  for protein and  $R^2=0.76$  for glucose,  $p < 0.001$ ; B:  $R^2=0.94$  for fat,  $R^2=0.92$  for protein and  $R^2=0.92$  for glucose,  $p < 0.001$ ).

## Discussion

The current study shows for the first time the relationship between gastric emptying and volume responses after ingestion of liquids of different macronutrient composition, their magnitude and dependency on posture, as well as the their effect on gastrointestinal perception in healthy volunteers. MRI combined with an optimised analysis method for nutrient liquid gastric emptying allowed a simultaneous, non-invasive and precise assessment of initial and late gastric volume responses, intragastric meal and air volumes and dynamics of gastric emptying in the seated (SP) and right decubitus (RP) body position. As expected, in all cases the postprandial stomach volume was larger than the ingested meal volume following meal infusion. Contrary to our hypothesis, gastric relaxation ( $V_{relaxation}$ ) and the increase in meal volume was larger after ingestion of glucose, resulting in higher stomach and meal volumes immediately after ingestion ( $V_0$ ). Glucose volumes remained elevated compared to fat and albumin during the early emptying phase ( $t_0-t_{45}$ ). Lower initial meal emptying and thus accumulation of secretion or swallowed saliva for the glucose meal may be responsible for this persisting elevation.<sup>179</sup> Various macronutrient are believed to activate separate and distinct mechanisms and pathways controlling motility, but all macronutrient induce gastric secretomotor function. The current data suggested a shorter latency of this response for glucose than for proteins and lipids. This fast inhibitory influence on initial gastric emptying by the glucose solution may be partially mediated by activation of osmosensitive afferent fibers, which are known to respond with a short latency (<7 sec) to hyperosmolar solutions.<sup>179,180</sup> For the fat and protein meal more complex metabolic processes are involved in the generation of a gastric inhibitory effect and these require several minutes to establish.<sup>181</sup> However, despite differences in initial gastric meal volumes, the dynamics of intragastric air increase were similar for each macronutrient. This indicates that the initial relaxation of the stomach is determined mainly by the resulting gastric meal volume load. How intragastric air may contribute to or modulate this process (possibly by altering intragastric pressure) is unclear.

The volume increase during the early gastric emptying period had similar characteristics for meal and stomach volume for both positions and for all test meals. The dynamics of intragastric air volumes were comparable for all macronutrient meals confirming that, primarily, the ingested meal volume and, secondarily, its change by gastric secretion and emptying (as reflected by different  $\kappa$  values of the LinExp model) were the major determinants of stomach volume response after intake of a caloric, liquid meal. Several gastric barostat studies have shown that macronutrient affect gastric tone with fat causing a rapid and most pronounced decrease in tone and therefore highest gastric volumes.<sup>174,182</sup> Assuming that different levels of gastric tone were present, the physical interrelation for volume and pressure implies that the similar stomach volume response in relation to the ingested meal volume reflects a macronutrient dependent difference in (initial) intragastric pressure. Since no direct information on gastric tone or intragastric (air) pressure was recorded in this study (due to its non-invasive approach), this hypothesis remains speculative and needs further validation. We conclude that macronutrient induced differences in gastric tone are not reflected as a distinct and specific volume response of the stomach under physiological non-invasive conditions.

After the meal/stomach volume increase over the first 20-30 min a posture independent, continuous emptying phase until 90 min was observed for all macronutrient. The higher

rates of gastric emptying, which occurred approximately after 40 minutes, for the fat meal in both positions were unexpected, since isocaloric meals of different compositions are known to have similar rates of gastric emptying.<sup>183</sup> Separation of the lipid emulsion in the intragastric environment, which can modify the spatial lipid distribution by flocculation causing layering can be a reasonable explanation for the faster emptying of the fat meal.<sup>39,184</sup> Intragastric creaming of an *in vitro* validated, acid stable (pH 2) fat emulsion - like the lipid solution used in this study - was also reported in a recently published study on the behavior of oil in water emulsions in the human gastric lumen.<sup>184</sup> This highlights that emulsion stability may not only be affected by low acidity, but also by other factors such as gastric lipolysis, which are responsible for 25 % of acyl chain hydrolysis during meal ingestion.<sup>185,186</sup>

Body position did not affect the nutrient related gastric volume responses due to initial meal emptying and secretion, and the subsequent meal emptying. The observation of unaltered meal emptying for carbohydrates is in accordance to other studies.<sup>100,137,138,187</sup> However, our study shows that intragastric air volume is altered by body position. In lying position intragastric air volume increased over postprandial time, regardless of ingested macronutrient, leading to a larger stomach volume at a late emptying phase compared to sitting. This increase could be reproduced in several studies of our group for different meals and could either suggest a more pronounced relaxation of the stomach during the late emptying phase or retained air in the stomach for this position.<sup>40,60</sup> To understand this phenomenon and its functional relevance concurrent intra-luminal pressure measurements are inevitable for future studies.

Although stomach volumes were different during the late emptying phase in RP, no differences in perception scores were detected. In both positions perception of satiety and fullness was linearly related to meal volumes for all macronutrient. This presumably reflects the activation of mechanoreceptors in the gastric body and fundus.<sup>37,188,189</sup> There were no significant differences in the symptom scores for fullness and satiety between the meals, which is compatible with the observed small differences in stomach volume. Perception scores for nausea reached only moderate levels with fat provoking the highest response. The volume versus fullness or satiety curve shifted to the left for the fat meal, while there was only a weak association between the sense of nausea and meal/stomach volume. All of these responses are possibly related to postgastric modulation of gastrointestinal sensations.<sup>174</sup> Overall the data on gastrointestinal perception suggest that the effects of isovolumic, isocaloric liquid meals with different nutrient composition effect gastrointestinal symptoms, at least in part, through postprandial gastric volume and nutrient specific postgastric modulation.

In summary, we showed that isovolumic and isocaloric liquid macronutrient meals modulate gastric volume responses by different initial meal emptying patterns and secretion. These initial effects, as well as meal emptying and perception, are independent of posture. Posture affects stomach volumes only during the late emptying period. The corresponding gastro-intestinal symptoms can be related, but not entirely explained, to the magnitude of postprandial gastric volumes. Hence, under non-invasive physiological conditions macronutrient specific accommodation responses, as shown in gastric barostat studies, are not reflected as gastric volume responses. To obtain an improved understanding of gastric volume responses and of symptom generation caused by different meal compositions, posture or other conditions (pharmaceuticals or in disease states), concurrent intra-luminal pressure measurements are needed for future studies.

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## Chapter 4

# Discussion, Conclusion and Outlook

### 4.1 Discussion and Conclusions

The projects presented in this thesis introduced the application of MRI in the field of pharmaceutical research and highlighted the use of MRI for research on gastric physiology. In these fields, the use of MRI is very limited so far, although the inherent advantages of MRI are potentially very favourable. In pharmaceutical as well as GI research, the most used imaging modality, i.e. the golden standard, is  $\gamma$ -scintigraphy and more recently also SPECT.<sup>32,34,163</sup> The most important advantage of MRI over these techniques is the capability of acquiring high resolution three-dimensional image data without the use of ionizing radiation and need for complex corrections of background noise and decay.<sup>30</sup> Repetitive studies in healthy volunteers are possible. Additionally, temporal (and spatial) resolution in dynamic and volume imaging is superior and better fits the requirements of human gastric motor function (scintigraphy:  $5 \times 5 \text{ mm}^2$  at 20 frames per minute vs. MRI:  $1.4 \times 1.4 \text{ mm}^2$  at 140 frames per minute).<sup>162</sup> Using SPECT for gastric volume imaging, the duration for the volume acquisition ranges from 3–7 min at an image resolution of  $3 \times 3 \text{ mm}^2$ <sup>163–165</sup> whereas on standard clinical MRI systems, this is achieved within 15–44 s at an image resolution of  $1.4 \times 1.4 \text{ mm}^2$ . Furthermore, neither separation of gastric contents and intragastric air nor simultaneous assessment of gastric volume and peristalsis is feasible using the nuclear imaging techniques.

### MRI in pharmacological research

In these studies and for the first time the feasibility of MRI to monitor oral drug delivery systems in vivo and the impact of formulation density and size and meal emptying on the dynamics and behaviour of gastric-retentive tablets in the human stomach was demonstrated. Labelled tablets performed as predicted and independent of meal consistency, emptying and time point of tablet administration. However, for each tablet formulation exceptions were observed, probably due to the large inter- and intra-individual variation in the gastric emptying process and the anatomical variability between subjects. Results on tablet behaviour in relation to density and size were in agreement with findings derived using  $\gamma$ -scintigraphy. A special emptying pathway of the aqueous *Gd*-DOTA drug model (along the inner curvature of the stomach) was detected for both seated and lying body position and induced a non-homogeneous mixing of drug model and meal. Such

inhomogeneous mixing of liquid and solid phases throughout the stomach represents an inherent limiting factor for the efficacy of orally administered substances that depend on the interaction with specific macronutrient.

There are limitations in the proposed approach for these studies. A key shortcoming of applying MRI is the limited number of methods for nutrient and drug labelling. Ongoing intensive research on the development of new and more flexible MRI contrast agents may help to overcome these limits in the future which may allow studies comparable to those with dual-isotope imaging.<sup>92</sup> Another shortcoming is the limited availability of the 0.5 T open-configuration MRI scanner used here, which allows the investigation in the seated position. However, it should be mentioned that this method can be applied to any 1.5 T compact clinical MRI system. In this case, the effect of posture on intragastric distribution must then be taken into account.<sup>42,44</sup>

Major conclusions for this first work are:

- MRI is useful for assessing the *in vivo* properties of orally ingested gastric-retentive tablets including their floating and sinking performance and drug release characteristics.
- *In vitro* or animal studies alone will not be sufficient to reliably predict intragastric fate and dynamics of oral drug delivery systems and thus also of the administered drugs in the human gastrointestinal tract. More extensive human studies are needed to collect a comprehensive knowledge about the fate of different drug delivery systems and applied drugs in the human body.
- In the presence of food, large sinking or floating tablets (size 19 mm x 8.8 mm) are very likely to remain in the stomach for over 4 hours. However, there is no guarantee that they will do so, and exceptions exist. It shows that the full stomach might empty solid particles with a size larger than 6 mm. Monolytic dosage forms of this size can not be regarded as safe gastro-retentive forms even in the presence of food.

The herein proposed MRI technique is not only restricted to study intragastric position and retention of tablets, but can be also applied for monitoring the position of drug dosage forms in the small and big bowel and determining their oro-cecal or oro-rectal transit times. It may also be useful for studying the gastrointestinal pharmacodynamic and kinetic behaviour of newly designed drugs or to evaluate existing drugs. However, further studies will be needed to evaluate if the technique may replace  $\gamma$ -scintigraphy for these purposes.

## MRI to analyse human gastric motor function

The studies demonstrated the effect of body position and different macronutrient on gastric motor function as assessed by MRI. It was the first time, GI studies simultaneously analysed the posture dependency of stomach, meal and intragastric air volume, gastric accommodation, gastric emptying, intragastric meal distribution and peristaltic frequency and velocity. Overall, the studies were aimed to improve and extend the understanding of the driving forces and the regulatory mechanisms of human gastric emptying. The effect of position on the rate of gastric emptying, the driving forces and regulatory mechanisms

has been extensively investigated over the last 40 years using various measurement setups and techniques.<sup>41–45,137–139</sup> This approach has produced conflicting results. Hence several aspects of the homeostatic emptying mechanism remain controversial. Recent studies using antro-duodenal manometry and concurrent duplex ultrasonography<sup>5,140</sup> or magnetic resonance imaging (MRI),<sup>4</sup> respectively, have suggested that the ‘pressure-pump’ mechanism is important in the gastric emptying of fluids. However, these studies were all performed in only one body position. Thus, this research could not clarify the relative importance of the ‘pressure-pump’ and the ‘peristaltic-pump’ during position change.

In the first study, gastric emptying and motor function was analysed in a radically altered body position, i.e. upside down (UDP), after ingestion of water and compared to the normal postprandial seated position (SP). Despite a drastic change in the intragastric distribution and fundamental change in the direction of forces, the rate of gastric emptying was similar in both positions. No correlation was found between gastric peristaltic activity and emptying rate. The emptying pattern was different between the positions, i.e. exponential for SP, but linear for UDP. This indicated an alteration in the driving forces of the emptying process. The exponential gastric emptying pattern observed for SP was dictated by the contribution of hydrostatic pressure to the emptying process. In UDP, where hydrostatic pressure acted against gastric emptying the dynamics of the linear gastric emptying pattern was likely due to continuous gastric tonic contraction maintaining a constant gastro-duodenal pressure gradient. In both positions, however, the rate of gastric emptying was most likely driven by gastric tonic contraction.

In conclusion, these findings provided further support to the hypothesis that the stomach rather resembles a ‘pressure pump’ (low-pressure tonic contractions of the stomach with the formation of a gastro-duodenal pressure gradient) than a ‘peristaltic pump’ (propagating high-pressure waves).

The second study aimed on determining the effect of right decubitus lying body position on relevant parameters of human gastric motor function in healthy volunteers. This was partly motivated by the fact that modern high-field MRI systems have horizontally aligned whole-body architecture only allowing measurements of organ function in the lying body position. This presents a limitation for gastric MRI, since several studies have shown that posture influences gastric function.<sup>41–45</sup> RP was chosen for imaging in the whole-body MRI system, because this body position provided the most similar stomach configuration compared to SP, i.e. the distal stomach was always filled with gastric contents and intragastric air was confined to the proximal stomach. Intra-individual comparison of stomach and intragastric air volume, intragastric meal distribution, gastric emptying and gastric peristalsis between RP and SP revealed an effect of body position on postprandial intragastric air volume. This induced different dynamics in the meal emptying, probably due to posture dependent vagal activity,<sup>158–161</sup> and resulted in a slightly larger meal volume for SP at time  $t = 90$  min. This subtle difference (20–30 ml) was not considered clinically relevant, since the changes observed for meal emptying in patients diagnosed with gastroparesis are of much larger extend.<sup>150</sup> However, considering the large inter-individual variation in the normal emptying process, this finding highlights the excellent sensitivity of MRI for the detection of small alterations in gastric function. No difference between the body positions was observed for gastric activity (mean peristaltic frequency) which provided further support for the hypothesis of a ‘pressure pump’ driven

gastric emptying process.

In conclusion, the current study demonstrates that MRI is a sensitive, non-invasive imaging technique for the measurement of gastric volume and motor function. Gastric MRI performed in the right decubitus lying body position is feasible for GI clinical research on gastric motor function and diagnosis of gastroparesis and gastric motility disorders. MRI has the potential to become the method of choice for the assessment of GI function in humans.

The aim of the third study was to study the effects of three different liquid macronutrient on gastric volume changes, related gastric emptying and on gastrointestinal symptoms using magnetic resonance imaging (MRI). The proposed hypothesis that changes in gastric tone for isovolumic and isocaloric liquid meals of different macronutrient content induce comparable gastric volume responses under non-invasive conditions questioned recent studies using the gastric barostat technique. These studies have demonstrated different effects on gastric accommodation and sensory responses following duodenal infusion of fat, protein or mixed nutrients during sustained gastric distension (mimicking the intragastric presence of food). The study was mainly performed in seated volunteers, however, to analyse the effect of posture on gastric volume response and emptying, additional measurements were performed in the right decubitus lying body position. Results showed that for both positions, initial (0–45 min) postprandial gastric volumes were highest for glucose. Initial emptying was different for fat and protein. The initial amplitude and dynamics of the volume curves for stomach and meal were uniform for all macronutrient and positions. Meal emptying was not affected by body position. Findings indicate that isovolumic and isocaloric liquid macronutrient meals modulate gastric volume responses by different initial meal emptying patterns and secretion. Data on gastric perception suggested that corresponding gastro-intestinal symptoms can be related, but not entirely explained, to the magnitude of postprandial gastric volumes.

In conclusion, under non-invasive physiological conditions macronutrient specific accommodation responses as shown in gastric barostat studies are not reflected as gastric volume responses. To obtain an improved understanding of gastric volume responses and of symptom generation under modulation by meals and posture or other conditions (pharmaceuticals or in disease states) concurrent intra-luminal pressure measurement data are needed for future studies.

## General considerations

The described methodological developments and also the future research projects outlined in the following section demonstrate the great potential of MRI in the field of GI research. So far, gastric MRI techniques have been applied almost exclusively in the study of basic physiology. However, very recent work has demonstrated the value of MRI in the clinical setting for diagnosis of motility disorders (e.g. gastroparesis, pylorospasm) and for monitoring response to treatment.<sup>190</sup>

The highlighted sensitivity of MRI may provide us with the means to define the clinical significance of a variety of motility disorders in a wide range of patients. Moreover, if these techniques prove to be reproducible and accurate, it may be possible to separate normal function from abnormal function by stressing the system under study by mechanical or pharmaceutical means. By assessing the functional response to a stressor, the range of

what would be normal may narrow. Thus the technique would not only have high sensitivity, but high specificity as well.<sup>191</sup> It has been proposed that the treatment of motility and functional GI disease should be aimed at correcting pathophysiological abnormalities.<sup>21</sup> MRI may identify relevant functional abnormalities and allow us to select specific treatments for the correction of these disorders and the alleviation of symptoms.

The presented studies were performed on 0.5 T and 1.5 T MRI systems. With the advent of high field MRI systems (3 T up to 7 T), not only in basic research, but also in the clinical environment, new possibilities may arise for more detailed and extensive investigations of GI function using MRI. An example is given in the following outlook section 4.2, discussing future research of brain function, using BOLD fMRI, in relation to gut motor and sensory function. Theoretically, the proposed methods are easily transferable to clinical 3 T MRI systems. However, there exists almost no experience for the use of high field MRI in GI research or diagnostic imaging. Although the increase in the signal to noise ratio (SNR) for higher field strength appears beneficial (lit), new methodological challenges (more inhomogeneous  $B_0$  field and increased signal absorption rates (SAR) due to higher RF fields) as well as physiological changes (altered longitudinal  $T_1$  and transverse  $T_2$  relaxation times of tissue and contrast agents (lit)) must be considered and investigated.

Despite many advantages of MRI compared to other medical imaging modalities, this powerful imaging tool is not without limitations. The technique is expensive and programming of dedicated imaging sequences requires specially trained personnel. The analysis and interpretation of gastric MRI images requires specialist skills and the reconstruction of three-dimensional (3D) gastric volumes is time consuming. In addition, the lack of a true standard of reference for comparison makes validation with existing methods difficult. At issue is not the “reality” of the images but the appropriate analysis and interpretation of the functional information provided by MRI. In GI research, recordings of the intraluminal pressures are essential for a complete understanding of GI motor function. So far, MRI is only feasible to detect relative pressures, i.e. pressure differences driving flow, by measuring spatially and temporally resolved intraluminal flow profiles. However, flow inside the GI lumen is very complex and solids and air within the chyme make flow measurement extremely challenging.

In summary, there is a large potential for the application of MRI techniques in the evaluation of GI physiology and a variety of motility disorders. The sensitivity of gastric MRI to physiological challenges has been shown, although more experience with these techniques must be gained in order to confirm the promise of this technique and to establish MRI in the clinical setting. In addition progress must be made in the automation of MRI image analysis, a process that is time consuming at present. If these issues are addressed, it could well be that MRI will replace existing investigations for the diagnosis and therapeutic monitoring of gastrointestinal motility disorders.

## 4.2 Outlook

In the following, selected future research projects in the field of basic gastric physiology are presented.

## Quantitative and dynamic assessment of intragastric dilution, mixing and distribution

Non-invasive concentration measurements of specific macronutrient or pharmacological substances in the gastrointestinal (GI) contents are of crucial importance for a more detailed understanding of the dilution, distribution and mixing processes and their influence on transport and emptying in the GI tract.

Paramagnetic contrast agents such as *Gd*-DOTA strongly affect the  $T_1$  relaxation time of an object's magnetisation due to molecular interaction.<sup>192,193</sup> The higher the concentration of the paramagnetic contrast agent the more  $Gd^{3+}$ -proton interaction and the shorter the  $T_1$  relaxation time. When using *Gd*-DOTA as meal label or water-soluble drug model the  $T_1$  relaxation time is shortest after meal ingestion or drug model administration and is decreasing over time due to dilution and mixing. By continuously measuring the  $T_1$  relaxation times of the luminal contents the quantitative and objective assessment of the concentration and therefore distribution and mixing of the drug model in the GI tract is feasible.

The aim of this project is to develop a rapid  $T_1$  mapping sequence (based on the technique proposed by Deoni et al.<sup>194</sup>) for the special use in gastric MRI allowing a dynamic and quantitative measurement of the in vivo concentration and distribution of an administered paramagnetic marker serving as a drug model. The technique will first be optimised and evaluated by in vitro experiments and then applied to in vivo studies. Using this technique, global and local effects on gastric juice production of the secretagogue pentagastrin and on gastric fluid volume reduction of PPI are investigated.

## Dynamic 3D gastric MRI and real-time imaging of gastroduodenal flow patterns and volumes

The detection and quantification of intragastric, transpyloric and duodenal flow patterns and profiles together with gastric motility, volume and pressure data would provide fundamental new insights into the interaction and contribution of motor mechanisms underlying gastric function. No medical imaging technique has yet been able to measure velocity profiles and flow volumes in the human gastroduodenal region. A mathematical model has been developed to simulate gastric flow and mixing and to study the degradation of orally administered tablets.<sup>195,196</sup> Simulations predicted characteristic fluid motions and mixing zones in the distal stomach and very low gastro-duodenal pressure gradients. It would now be interesting to physiologically evaluate this model, include pyloric activity and extend it to three dimensions. Therefore, "four-dimensional" data acquisition with good spatial as well as temporal resolution of the total human gastroduodenal region is required. MRI is the most promising medical imaging method to achieve this ambitious goal.

MRI has been applied for dynamic 3D cardiac imaging and for the detection of small vessel and coronary flow patterns and/or profiles.<sup>197–201</sup> These techniques are very promising for the application in this specific GI research topic. However, anatomical and physiological conditions are somewhat different for gastric MRI, due to slower velocities, irregular tissue motion and the current difficulties with GI myoelectric triggering. Real-time imaging of fluid movements in the gastric lumen and through the pylorus would be ideal, but this is technically very demanding and a trade-off between image quality (signal to noise ratio (SNR) and image resolution) and acquisition speed must be made. The advent of two-

dimensional RF excitation pulses, sophisticated reduced k-space acquisitions (kt-BLAST or kt-SENSE) and parallel imaging techniques for high-field MRI (SENSE, GRAPPA, PRESTO) enable high resolution real-time imaging with appropriate SNR and simultaneous flow encoding.<sup>202–205</sup>

The aim of this project is to adjust and apply the proposed rapid MRI methods for the 3D dynamic imaging of gastric volumes and gastroduodenal flow. The accuracy/sensitivity and reliability of these techniques will be assessed *in vivo*. Gastroduodenal flow patterns and related gastric motility and emptying of various liquid test meals will be assessed in healthy volunteers. Pharmacological modulation will be applied to investigate the effect of changes in gastric tonic activity on the gastroduodenal flow patterns.

## Strain mapping

Tagged MRI with spatially encoded magnetic saturation planes together with harmonic phase (HARP) analysis is used in cardiac imaging to determine maps of motion and mechanical strain, describing regional function of the heart.<sup>206,207</sup> A similar approach might be used to map strain and stress of the gastrointestinal wall (and also fluid motion) and correlate it to gastric motor function. However, the short  $T_1$  relaxation time of the gastrointestinal wall ( $\sim 500$  ms) narrows the motion detection window and reduces the sensitivity of the technique. Nevertheless, the rapid detection of fluid motion of ingested intragastric liquids with appropriate  $T_1$  relaxation time using tagged MRI seems promising.

Recently, a novel US Doppler method for strain rate imaging (SRI) was introduced to estimate strain in moving gastrointestinal tissue in humans.<sup>208</sup> Biomechanical events in the inner circular and outer longitudinal muscle layer of the antral wall could be discerned. It was found that the circular layer constituted the driving force during contraction and outer layer passively followed the movement during phase II contractile activity. The US technique, however, is limited by the same factors as routine gastric US (bowel gas, abdominal fat) and a strong angle-dependency because the strain rate can only be measured in the US beam direction. Theoretically, similar measurements may be feasible using MRI; however as yet only an indirect assessment of gastric strain and pressure force has been acquired by this technique by observing the mechanical action of the antrum on agar beads with a range of fracture strengths.<sup>209</sup>

## Visceral Sensitivity and the Central Control of GI function

The current hypothesis that functional gastrointestinal disorders result from dysregulation of afferent and efferent communication between the gut and the brain has led to a growing interest in the research of brain function in relation to gut motor and sensory function. The most popular MRI technique in this field is blood oxygen level dependent (BOLD) ‘functional’ MRI (fMRI). This technique is based on the effect that the MRI signal allows the detection of different concentrations of oxyhaemoglobin and deoxyhaemoglobin in tissue or vessels. Visceral stimulation locally increases blood flow in activated areas of the brain, increasing the concentration of oxyhaemoglobin in several regions of interest. Studies have shown that visceral/gut sensation involves activation of several brain regions that are associated with various brain functions, including sensation, cognition, and affect.<sup>210</sup> Recent evidence from BOLD fMRI suggests that CNS activity in response

to visceral stimulation is altered in functional bowel disease. Also, the emotional cortex seems to respond in an abnormal, exaggerated fashion to GI stimulation.<sup>211,212</sup> The complexity of the brain response to visceral stimulation makes studies of brain function in patients with functional gastrointestinal disorders difficult and demands great caution in interpreting their results. Moreover, there are methodological limitations in the BOLD fMRI technique, in particular the small MRI brain signal difference of only 1 % to 5 % between the basal and the activated state.

Looking in the future however, ultra-high-field BOLD fMRI with higher signal to noise ratios offer the opportunity for the objective measurement of visceral sensation and a better understanding of the role of the central nervous system in conducting and processing visceral signals. Furthermore, ultra-high-field MRI scanners may also enable high-resolution magnetic resonance spectroscopy (MRS) to monitor the metabolism of specific neurotransmitters in the brain and, potentially, in the spinal tract and enteric nervous system.



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# Curriculum vitae

I was born on June 26<sup>th</sup> 1973 in Kaiserslautern (Pfalz, Germany) as son and the second child of Monika (nee Mayer) and Jürgen Steingötter. In Kaiserslautern, I attended primary and secondary school and the Gymnasium (Hohenstaufen-Gymnasium) where I finally graduated with a german *Abitur* in June 1992.

Starting fall 1992, I was enrolled for one year as extra-mural student at the Technical University (TU) of Kaiserslautern (Germany) where I passed the exam in Higher Mathematics for Engineers I and II. In October 1993, I started my studies in Electrical Engineering at the TU of Darmstadt (Germany). I moved to the University of Karlsruhe (TH) (Germany) in fall 1995 to continue my studies with specialization in Biomedical Engineering. An internship in microelectronics gave me the opportunity to spend 5 month (from October 1996 to March 1997) at the National Microelectronics Research Centre (NMRC) in Cork, Ireland. In the following, I joined the cardiac research group of Prof. O. Dössel, head of the Institute of Biomedical Engineering (IBT) at the University of Karlsruhe, to perform a student research project on medical image processing and to work as student assistant. In Summer 1999, I started my *Diplomarbeit*, the german equivalent to the Anglo-Saxon Masters thesis, at the cardiac mechanics research group (CMRG) at the University of California, San Diego (UCSD), USA, supervised by Prof. A.D. McCulloch and Prof. O. Dössel. Topic of my thesis work was the development of “a structural model of atrial anatomy in the pig”. Subsequently, I received my *Diplom* in Electrical Engineering from the University of Karlsruhe (TH) in March 2000.

In July 2000, I joined the MR group of Prof. P. Bösiger at the Institute of Biomedical Engineering (IBT), University and Swiss Federal Institute of Technology (ETH) Zurich (Switzerland), as PhD student and teaching and research assistant. My research work was focused on applying “MRI for the analysis of human gastric motor activity, intragastric distribution and related emptying”. Research projects were performed in very close collaboration with Dr. Werner Schwizer of the functional research group at the division of Gastroenterology at the University Hospital Zurich, headed by Prof. M. Fried.

Besides my research work, I primarily indulge in mountaineering, climbing, ski-touring, soccer, cycling, music, reading and cooking.